VOLUME 61 NUMBER 3

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SEPTEMBER 1950

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $14.00

Entered as Second Class Matter July 10, 1925, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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Beginning with the October 1950 issue, it is planned to introduce several changes in the covers of all the A. M. A. specialty journals.

The cover of this journal will be white enamel stock with title identification as the A. M. A. Archives of Surgery in color, with date, volume and number also in color. The Table of Contents, which is now carried on the back cover, will be placed in the front of the journal directly preceding the lead article or editorial. Second, third and fourth covers will be used for color advertising.

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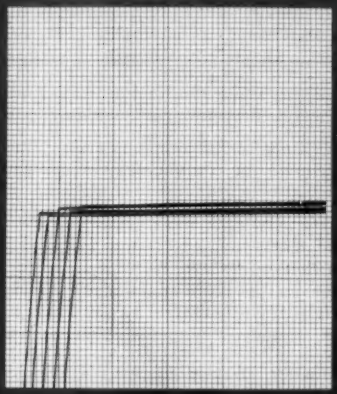

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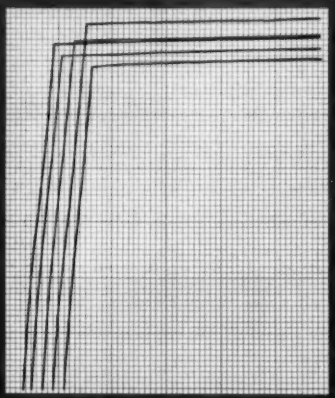

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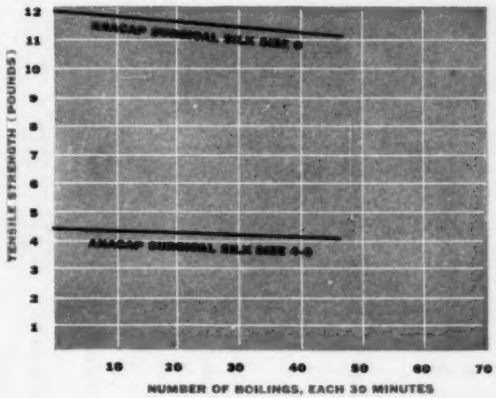

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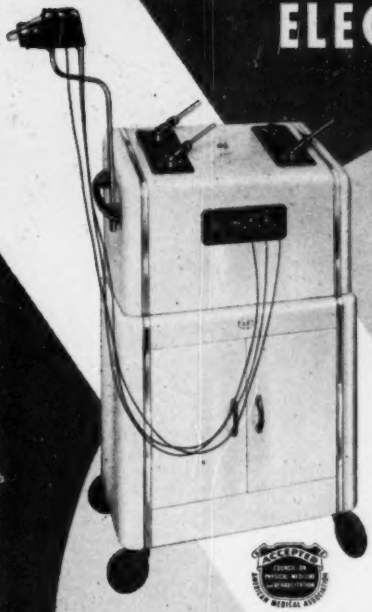

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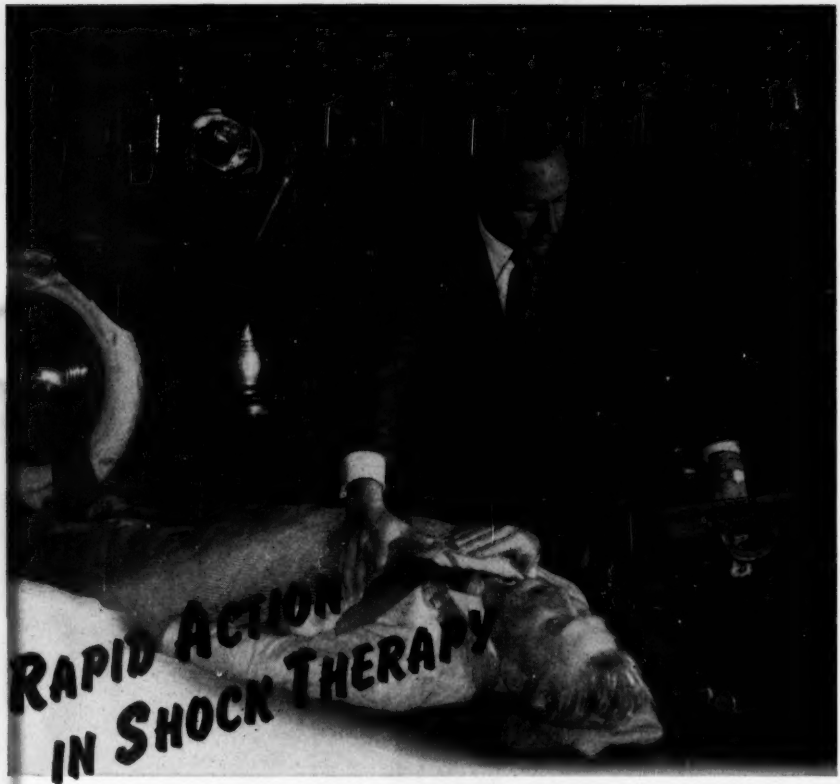

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References: Heyl, J. T., et al. THE EFFECT OF CONCENTRATED SOLUTIONS OF HUMAN AND BOVINE SERUM ALBUMIN ON BLOOD VOLUME AFTER ACUTE BLOOD LOSS IN MAN. Jour. Clin. Invest. 22: 763 (1943)

Woodruff, L. M. and Gibson, S. T. THE USE OF HUMAN ALBUMIN IN MILITARY MEDICINE: THE CLINICAL EVALUATION OF HUMAN ALBUMIN. U. S. Nav. Med. Bull. 40: 791 (1942)

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SLUDGED BLOOD FOLLOWING SEVERE THERMAL BURNS

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THE PURPOSE of this paper is to report the presence and to discuss the significance of sludged blood following severe thermal burns. Three sets of pathologic mechanisms are proposed: (1) a mechanism for the production of burn shock, (2) a mechanism for the production of postburn anemia and (3) a mechanism seemingly capable of being at least a factor in the postburn "toxemia."

GENERAL PROBLEMS

The pathologic alterations in the physiology of mammals following thermal burns have been attributed to almost as many factors as there have been investigators in the field. However, in spite of a great deal of accumulated experimental data, the factors determining the altered physiology of human patients during the first twenty-four to seventy-two hours following a severe burn continue to present important clinical problems. Prior to the introduction of tannic acid therapy by Davidson in 1925, the mortality rate within the first forty-eight hours after burn averaged 64 per cent.[1] The two most significant kinds of complications

This work was aided by grants from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago, from the Ella Sachs Plotz Fund.

From the Department of Surgery and the Hull Laboratory of Anatomy, University of Chicago, and the Department of Anatomy, Medical College of the State of South Carolina, Charleston, S. C.

The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Chicago.

1. (*a*) Harkins, H. N.: The Treatment of Burns, Springfield, Ill., Charles C Thomas, Publisher, 1942. (*b*) Salvioli, J.: Ueber die Todesursachen nach Verbrennung, Virchows Arch. f. path. Anat. **125**:364-397, 1891. (*c*) Vogt, E.: Versuche über die Uebertragbarkeit des Verbrennungsgiftes, Ztschr. f. Exper.

(Footnote continued on next page)

occurring in this early period after burn are (1) "shock" and (2) "acute toxemia." Some of the basic physiologic and/or pathologic mechanisms capable of producing these complications have remained unknown and are the chief considerations of the experiments herein reported.

MATERIALS AND METHODS

Rabbits and dogs were used as experimental animals. One severely burned human being was also carefully studied,[2] and, from time to time several other severely burned patients were briefly observed. The rabbits were obtained from two commercial breeders and the dogs from the Chicago Municipal Dog Pound. All experimental animals were kept sufficiently long before use to insure that their nutritional state was good.

The experimental procedures were intended for the study of pathologic changes in the circulating blood, blood flow and vessel walls. Hence it was necessary to review the known characteristics of healthy normal blood and vessel walls. Further, it was necessary to determine that each of our experimental animals used had normally circulating blood and normal vessel walls when the experiment began and that the control animals, equally anesthetized but unburned, continued to have normally circulating blood and normal vessel walls. The microscopically visible, specific characteristics of healthy normal blood and vessel walls have previously been determined by observations[3] made in great numbers of frogs, salamanders, mice, rats, guinea pigs, cats,

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Path. u. Therap. **11**:191-222, 1912. (*d*) Wilson, W. C.: Treatment of Scalds and Burns by Tannic Acid, Brit. M. J. **2**:91-94 (July 21) 1928. (*e*) Seeger, S. J.: The Treatment of Burns, in Lewis' Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 1, chap. 14.

2. Knisely, M. H.; Bloch, E. H.; Eliot, T. S., and Warner, L.: Sludged Blood, Science **106**:431-440 (Nov. 7) 1947.

3. (*a*) Knisely, M. H., and Bloch, E. H.: Intravascular Agglutination of Erythrocytes in Disease, with Cinema Demonstration, Proc. Inst. Med. Chicago **15**:281 (March 15) 1945. (*b*) Knisely, M. H.; Eliot, T. S., and Bloch, E. H.: Sludged Blood in Traumatic Shock, Arch. Surg. **51**:220-236 (Nov.-Dec.) 1945. (*c*) Knisely, M. H.; Stratman-Thomas, W. K.; Eliot, T. S., and Bloch, E. H.: Knowlesi Malaria in Monkeys: I. Microscopic Pathological Circulatory Physiology of Rhesus Monkeys During Acute Knowlesi Malaria, J. Nat. Malaria Soc. **4**:285-300 (Dec.) 1945. (*d*) Knisely, M. H.; Bloch, E. H.; Brooks, H. F., and Warner, L.: Microscopic Observations of the Circulating Blood of Nine Healthy Normal Horses, All of Which Had Unagglutinated Circulating Blood Cells and High *In Vitro* Erythrocyte Sedimentation Rates, Am. J. M. Sc. **219**:249-267 (March) 1950. (*e*) Knisely, M. H.; Bloch, E. H., and Warner, L.: Selective Phagocytosis: I. Microscopic Observations Concerning the Regulation of the Blood Flow Through the Liver and Other Organs and the Mechanism and Rate of Phagocytic Removal of Particles from the Blood, Det Kongelige Danske Videnskabernes Selskab, Biologiske Skrifter, Copenhagen, 1948, vol. 4, no. 7. (*f*) Knisely and others.[2]

dogs, horses, rhesus monkeys and human beings. These characteristics are as follows:

1. Erythrocytes are not agglutinated.

2. Leukocytes do not stick to healthy, normal, undamaged endothelial vessel linings.

3. The flow of unagglutinated blood is laminar or streamlined.

4. Small vessels, in most parts of the body, do not leak fluid rapidly enough to cause microscopically detectable hemoconcentration of the passing blood or edema of the tissues beside the small vessels.

5. The flow in most vessels 60 to 100 microns in diameter is so rapid that at magnifications of × 48 to × 64 individual erythrocytes cannot be seen. This is a crude but accurate and useful criterion for adequate rates of blood flow through most open tissue capillaries. If the rates of flow of oxygen-saturated arterial blood are fast enough so that individual unagglutinated blood cells cannot be seen in vessels this size in animals and men, higher magnifications show that no visible hemoconcentration is taking place in true capillaries, i. e., almost no blood fluid is being lost through the walls of tissue capillaries.

6. The shapes and dimensions of the vessels of the peripheral vascular beds constitute a perpetual bottleneck in the circulatory system. All the vessels which carry blood toward tissues are long, narrow, slowly tapering, truncated cones. When arterioles branch, each branch has a narrower lumen than the parent stem. The capillaries or sinusoids which carry blood through tissues are approximately cylinders, and the veins are slowly widening cones again. Arteriovenous anastomoses have been found in some tissues, but these have small total surface areas; if oxygen, glucose and other blood-borne anabolites are to be distributed effectively to the cells of a tissue, the blood must flow through the capillaries or sinusoids of that tissue.

In the internal organs of the mammals which we examined the open arteriole tips were for the most part narrow enough so that every red and white cell passing through was forcibly distorted—usually pinched and elongated or folded. This distortion is also clearly shown in frogs in a motion picture prepared by Fulton and Lutz [4] in 1941. The capillaries through which blood is flowing normally vary from a little less than once to as much as two to two and a half times the diameters of the passing red cells. Most true capillaries can dilate without losing tonus, weakening and sacculating to a little more than two or two and a half times the diameters of the animal's own red cells.

4. Fulton, G. P., and Lutz, B. R.: The Neuro-Motor Mechanism of the Small Blood Vessels of Rana Pipiens (Motion Picture), abstracted in Anat. Rec. **79**:23 (March) 1941.

These statements are true of the arterioles and capillaries of the bulbar conjunctiva of human beings, whose red cells are usually a little less than 8 microns in diameter, and almost certainly true of all the arterioles and capillaries of most human organs during life. Thus, as is well known but not always remembered, under all conditions of health and disease the arterioles and capillaries are a perpetual bottleneck in the vascular system.

These specific characteristics of circulating normal blood were also found to be present in our healthy normal rabbits and dogs. Further, in the experiments to be described, only those animals were used in which the circulating blood and vessel walls exhibited the aforementioned characteristics.[5] In our experience the importance of and even the necessity for the presence of normally circulating blood and normal small vessel walls as evidence for a healthy normal animal cannot be overemphasized.

A group of rabbits was encountered, for example, in which, though they appeared well fed and were without clinical signs of disease, the circulating blood was seen to have intravascular agglutination of red cells, slowed rates of blood flow and white cells sticking to sacculated vessel walls. These animals were discarded for use in the burn experiments and at autopsy were found consistently to be heavily infested with metazoan liver parasites.[5b]

One other important aspect of the circulation of healthy normal animals has been studied only in frogs and in rhesus monkeys. During prolonged observations of the living livers of these animals, the normal naked red cells have been seen to slide and bump along the inner surfaces of the highly phagocytic cells which line the hepatic sinusoids, but no normal naked red cell has ever been observed to be ingested. In contrast, in rhesus monkeys during stage II of malaria caused by Plasmodium knowlesi the parasitized red cells are coated with an easily visible, photographable precipitate [3e] which holds these parasitized red cells together in small clumps. By direct microscopic observation in the living liver, these clumps of coated, parasitized red cells have been observed being selectively phagocytosed from the blood flowing through the hepatic sinusoids. They were ingested by the phagocytic, sinusoid-lining, von Kupffer cells. During this process the monkey's unparasitized, uncoated erythrocytes were entirely ignored by these stationary phagocytes. (For details of these and similar observations, see Knisely and others.[3c,e])

5. (*a*) Clark, E. R., and Clark, E. L.: Observations on Changes in Blood Vascular Endothelium in the Living Animal, Am. J. Anat. **57**:385 (Nov.) 1935. (*b*) Knisely, M. H.; Bloch, E. H., and Warner, L.: Microscopic Observations of Living Blood and Vessel Walls Are a Necessary Part of the Preselection of Normal Animals for Biological Experiments, Anat. Rec. **94**:550 (March) 1946.

Two methods were used to observe the circulating blood and small vessels during the following burn experiments. In one the bulbar conjunctiva and/or nictitating membrane of rabbits and dogs was obliquely illuminated with the use of a Sluhan ophthalmoscopic lamp. The vessels in these tissues were then observed with a biobjective, binocular, "Greenough type," stereoscopic, dissecting, Leitz microscope, which gives magnifications of × 32, 48, 64 and 96. This method has been demonstrated publicly to the members of the American Association of Anatomists.[6] Because of the thorough mixing of the blood in the heart and because of the anatomy of the arch of the aorta and the vessels branching from it, the circulating blood observed by this "eye method" continuously is a statistically valid sample of all the animal's circulating arterial blood.[6c] The method permits study of statistically valid samples of the circulating blood of an animal which has not been subjected to any traumatic experience or operation.

The other method was the fused quartz rod method, previously described,[7] which permits many tissues and internal organs of anesthetized animals to be transilluminated and studied microscopically in vivo.

A total of 12 dogs and 18 rabbits were preselected by microscopic observation of the circulating blood in small vessels of the bulbar conjunctiva, anesthetized, observed, then severely burned and observed again. Each animal therefore served as its own control for the effects of anesthesia and burning.

In some animals the circulating blood and vessel walls were studied only by observing the bulbar conjunctiva; in others, opened by laparotomy at intervals after burning, the circulating blood and small vessels of omentum, mesentery and intestinal walls were also studied. By using both methods of observation on the same animal, it was possible (1) to

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6. (*a*) Knisely, M. H., and Bloch, E. H.: Demonstration of the Method and Apparatus Currently Used in Making Microscopic Studies of the Circulating Blood and Local Vessels of the Bulbar Conjunctiva of Living Unanesthetized Human Beings, Anat. Rec. **100**:132 (April) 1948. (*b*) Knisely, M. H.; Bloch, E. H.; Eliot, T. S., and Warner, L.: Blood: Circulating; Method and Apparatus, in Glasser, O.: Medical Physics, Chicago, The Year Book Publishers, Inc., 1950, vol. 2, pp. 129-130.

6c. Knisely, Bloch, Eliot and Warner.[2] Knisely and Bloch.[6a]

7. Knisely, M. H.: A Method of Illuminating Living Structures for Microscopic Study, Anat. Rec. **64**:499, 1936; The Fused Quartz Rod Method of Illuminating Living Structures for Microscopic Study: McClung's Microscopical Technique, New York, Paul B. Hoeber, Inc., 1938; Fused Quartz Rod Method of Illuminating Living Structures for Microscopic Study (This is a Statement of the Uses and Purposes of the Method), in Cowdry, E. V.: Laboratory Technique in Biology and Medicine, ed. 2, Baltimore, Williams & Wilkins Company, 1948. Knisely and others.[3c] Hoerr, N. L., in Glasser, O.: Medical Physics, Chicago, The Yearbook Publishers, Inc., 1944, pp. 625-627.

have control observations of the effects of anesthesia and laparotomy, (2) to check the validity of the sample of the circulating blood observed by either method as a sample of the generally circulating blood and (3) to differentiate the effects of laparotomy and of burning by allowing intervals between them.

The intervals between burning and opening an animal permitted the pathologic changes resulting from burn to accumulate and maximize before the laparotomy was performed. This control was necessary since laparotomy may, if not carefully done, cause the type of sludge produced by mechanical trauma.[3b, d] By the use of delay periods of various lengths, such as three hours, six hours and twelve hours, between the burning and the laparotomy, the sludge induced by laparotomy trauma was prevented from complicating the pathologic postburn condition which we intended to study.

By observing the bulbar conjunctiva before and after each of the procedures (anesthesia, laparotomy and burning), it was possible to establish the effects of each of these procedures on the circulating blood and vessel walls. By making observations, after anesthesia and laparotomy but before burning, of both the externally situated bulbar conjunctiva and the internally situated omentum, mesentery and intestinal wall, it was possible to establish (1) the effects definitely attributable to burning, as opposed to the effects of laparotomy, and (2) the equal validity as areas for study of the circulating blood and vessel walls of the bulbar conjunctiva and the circulating blood and vessel walls in the omentum, mesentery and intestinal wall.

We thus had controls on (1) each animal used, (2) the effects of anesthesia, laparotomy and burning either separately or when present in combination, (3) each of the methods of observation used and (4) the validity of the samples observed as statistically valid samples of the blood circulating throughout the entire body.

Some of the animals died spontaneously, and some were killed at two to three hour intervals up to twenty-four hours and at twelve hour intervals between the twenty-fourth and seventy-second hours after the burn. From the animals killed, portions of spleen, liver and bone marrow were taken for histologic study. The intervals for killing and taking tissues for histologic sections were chosen in an attempt to determine how soon after the burning red cells could be observed in phagocytes and for how long a period after the burn ingested but undigested red blood cells could be seen in such phagocytes.

In addition to these observations in experimental animals, one severely burned human being was studied by the "eye method." She had been accidentally burned by the explosion of about a gallon of boiling alcohol. She was burned over the backs of the thighs and the backs of the forearms and hands. There were no burns close to her eyes. She

was observed within the first hour after she was burned, then at approximately fifteen to twenty minute intervals during the first eight hours following burn and at irregular intervals thereafter for fifteen days.

The animals were anesthetized with Abbott's veterinary pentobarbital sodium, given subcutaneously between the scapulas. This drug was used because (1) it had been established that it does not cause intravascular agglutination of the blood of rhesus monkeys or dogs or microscopically detectable changes in their vessel walls even when the animals are kept anesthetized for twelve to fourteen hours and (2) in anesthetic doses it did not prevent either mechanical trauma or P. knowlesi from initiating an intravascular agglutination which changed the blood to a thick sludge. In brief, pentobarbital sodium did not itself form a sludge or prevent sludge from being formed.

No animal was burned until it was in deep anesthesia.

The method of burning, though not completely standardized, consisted of direct application of a red-hot copper soldering iron from the axillas to the groins of each animal. The area burned was estimated to be approximately 30 per cent of the body surface. The degree of burning induced was roughly comparable to the second degree burn of human beings.

The tissues burned were thus over the chest and the abdominal wall. No burn was deep enough to cause visible injury on the inner surface of the body wall; in no experiment were the underlying, intra-abdominal structures, such as stomach or intestine, directly heated. The injury was produced in one anatomic area, but the blood was observed flowing through the vessels of other, anatomically distant areas. Thus, this most significant point was accomplished: The observations showed generalized effects of the burn occurring at considerable anatomic distances from the area which had been directly burned.

Since the area burned was the anterior body wall, it is evident that the circulating blood observed had to pass from the burned area back to the right side of the heart and out into the general systemic circulation before being observed. Because of this generalized distribution (resulting from the thorough mixing of the blood in the heart and guaranteed by the anatomy of the arch of the aorta and the branching patterns of the vessels from it), the circulating blood observed both in the bulbar conjunctiva and the nictitating membrane and in the small vessels of the intestine continually represented a statistically valid sample of all the animal's circulating blood. The validity of this sampling method has previously been pointed out.[8] Thus, the results to be reported were occurring with but minor local modifications all over the unburned portions of the body.

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8. Knisely, Eliot and Bloch.[8b] Knisely and Bloch.[6] Knisely and others.[6c]

In one series of experiments made, using dogs, motion pictures were taken through the microscope, recording on Kodachrome film many of the changes about to be described. This motion picture has been publicly shown to physicians and medical scientists.[9]

Since a special type of sludge and specific types of pathologic vessel wall reactions were constantly found after the burns, a brief statement of terminology used in describing sludges and small vessel reactions is here introduced, which permits the terminology of this paper to be in conformity with that of other reports, and, what may be more important, permits the specific characteristics of burn sludge to be compared with blood sludges resulting from initiating factors other than burns.

Knisely and Bloch[3a] and Knisely, Bloch, Eliot and Warner[2] reported a survey in which more than 1,000 hospital patients, for whom over 50 different clinical diagnoses were made, were each found to have intravascular agglutination of the circulating blood. The masses of which these different blood sludges were composed were not rouleaux. They were larger and more rigid than the familiar serpentine rouleaux. Further, the largest masses caused easily visible permanent emboli which plugged terminal human arterioles.

Two general separate and distinct types of blood cell masses have been recognized in these studies:

(1) Those which do not break up into smaller parts as they are carried into and forced down through the long, progressively narrow, cone-shaped arterioles, the terminal arterioles and the narrow, cylindric capillaries. By arbitrary definition, these masses which do not break up have been named the basic masses of a sludge, usually abbreviated, particularly in conversation, to "the basics." By means of high speed flash photography, each exposure lasting approximately 1/2000 second, the fact that the basics are present in arteries has been recorded in colored still pictures (see *Life* magazine of May 31, 1948). Further, the basic masses can be seen in arterioles in the scenes following titles no. 28, 65 and 77 in the motion picture "Knowlesi Malaria in Monkeys."[3c]

(2) Cohering aggregates of basic masses. These aggregates frequently or ordinarily are considerably larger than the basic masses of which they are composed. The aggregates do break up into smaller parts as they are forced down through long, cone-shaped arterioles. Each such aggregate breaks up into its own component basics when it passes through an arteriole and/or capillary. And in many patients the basics

9. Dragstedt, L. R.; Brooks, F.; Knisely, M. H., and Warner, L.: Physical Alterations in Circulating Blood Following Burns, Proc. Am. Federation Clin. Research **2**:108-109, 1945. Brooks, H. F.; Dragstedt, L. R.; Warner, L., and Knisely, M. H.: The Sequence of Circulatory Changes Following Severe Thermal Burns, Anat. Rec. **100**:644 (April) 1948.

so released reform in new combinations, into new "charge aggregates," as they are carried into small venules in which the blood is flowing slowly.

The presence and behavior of both "basic" masses and "charge aggregates" after the burns will be described.

E. R. and E. L. Clark [8a] described the responses of the walls of small vessels in terms of increasing degrees of visible response to increasing degrees of severity of injury. Their paper should be studied with care by all who are seriously interested in living pathologic physiology, for the degrees of the vascular responses visible are direct indicators of the degrees of damage already suffered at any given time by the visible vessels. A number of subdivisions can now be added to the original descriptions by the Clarks. The phases described by them and the subdivisions which we would add are as follows:

1. When the endothelium and circulating blood are completely healthy, no white cells stick to the inner surface of the endothelium.

2. After mild injury there is a temporary [few seconds] sticking of leukocytes to the vessel lining.

3. A prolonged [many seconds] sticking of leukocytes occurs. During this phase there is, however, no emigration of the leukocytes outward through the vessel wall. To this phase we would add two subdivisions, phases 3a and 3b.

3a. Leukocytes almost completely cover the inner surface of the walls of small vessels and may stick in one place for hours.

3b. The leukocytes are two or more layers deep, covering the inner surface of the walls of small vessels, and stick for hours. During phases 3a and 3b, no emigration of the white cells through the vessel walls occurs.

4. There is a more prolonged sticking of leukocytes, with the emigration of some through the vessel walls. To this phase we would add a phase 4a.

4a. This phase consists of a relaxation and dilatation of small vein walls. Sausage-shaped relaxed segments develop in the vein walls, just as a hyperdilated bulge develops in an automobile inner tube at a weakened point when it is overinflated while outside the tire. Such vessel segments are often said to be "sacculated." When long segments of veins have become sacculated, it is easy to see that they have not only become wider but definitely have increased in length. They may become tortuous. During this phase, white cells may or may not be stuck to the inner surface of the vessel wall and there may or may not be visible leukocyte emigration through the vessel wall.

Usually, but not always, the pathologically relaxed walls of such dilated, sacculated vessel segments are highly permeable to all, or nearly

all, the fluid portions of the blood plasma. Such segments may have whole blood coming in one end, fluid leaking out through the vessel wall and a thick blood cell paste passing out through the efferent end of the vessel. Relaxed, dilated segments may have blood moving through them for reasonably long periods or they may become plugged or thrombosed after intervals of various lengths.

Persons who study such vessels with microscopes may say that "stasis" has developed or that the small vessel is thrombosed. If great numbers of such vessels are present in a tissue and seen grossly, the observer may say that the vessels of the tissue are "congested."

5. Phase 5 consists of localized extravasations of erythrocytes, with partial collapse of the previously bulged endothelium.

Every phase of the response of vessel walls to injury thus far described is completely reversible to a healthy normal condition of vessel walls within a reasonably short period, provided that (*a*) the stimulus to which the pathologic response is occurring is withdrawn and (*b*) healthy normal blood flows through this vessel again at normally rapid rates.

5a. During this phase, small hemorrhages occur through the walls of injured endothelium, letting small to moderate amounts of blood out into surrounding tissues. Immediately after such a hemorrhage, the hole through the vessel wall is sealed and the vessel wall seems intact when examined with a microscope during life. Furthermore, there are no visible evidences of continuing leakage around the point which has been thus reconstituted.

6. Phase 6 consists of complete disintegration of the endothelium from which there is no recovery. A new blood supply can reach local areas of tissues after this phase only by regrowth of new vessels, that is, by revascularization of the tissue.

RESULTS

After the burns essentially the same changes in the circulating blood were observed in all the animals, both rabbits and dogs, and in the human patient. The changes were the same whether the observations were carried out in the vessels of the bulbar conjunctiva and/or in the animal's omentum, mesentery and vessels visible in the outer layers of the intestinal wall. The results are presented in five sections in the chronologic order of their appearance.

After the Burn.—A. Visible Changes in the Blood: 1. Almost immediately, as early as one to two minutes after the burn, clumps of red blood cells could be seen in all visible arterioles, capillaries and postcapillary venules (cinema recorded). Each individual clump was different from an individual red blood cell. Each was much larger and darker

colored than are individual red cells. The tissues, blood and vessel walls were examined at stereoscopic magnifications of × 48 and × 96. At × 48 individual red blood cells cannot be seen. At least × 96 is necessary to make individual red blood cells clearly visible. With the use of both magnifications, there could be no doubt but that the clumps were tightly agglutinated masses of red blood cells. At × 48 the large individual masses could easily be observed as individual entities turning and tumbling in the pinkish stream. These clumps are the "basic masses" of the burn sludge.

Throughout all our observations following burn, the basic masses of the sludge have shown certain specific characteristics. The masses were spheres or short rods. The surface of each mass was glassy smooth, and they were extremely rigid.

A 16 mm. motion picture was taken through the microscope in a dog, recording the passage of basic masses through the smallest-sized vessels. A strip of this film, approximately 20 feet (609 cm.) long, was spliced together end to end, forming a loop which could be projected continuously. Prolonged projection of the film gave a chance for repeated study of processes going on in one area. It showed that the basic masses of the sludge in a burned dog were for the most part nearly spherical or were short round-ended rods like short bacilli. The rod forms lined up, of course, so that their long axes were parallel to the long axis of each narrowest vessel through which each mass was passing.

There was a much higher percentage of spheres among the masses than of short rods. The diameters of the rods and the diameters of the spheres were approximately equal.

The surface of each basic mass after the burn was glassy smooth. This appearance is in contrast to that of the basic masses in other pathologic conditions, such as, for instance, those following mechanical trauma to a man or a dog. After severe crushing injury to striated muscle of men and dogs the basic masses formed may be fluffy, and they may appear to be tacky or sticky.[10]

The hard, glassy smooth masses formed after burn may cohere but still roll around on each other. As a simple analogy, consider behavior of highly magnetized steel spheres which may cohere but can, while cohering, roll each on the others. In contrast, in some of the sludges formed in dogs after crushing injury, the basic masses stick to each other by whatever surfaces come in contact, as would two hands full of plasticene, wet clay or putty.

For a while after the burn the basic masses formed in an animal did not show much tendency to stick to each other.

10. Knisely and others.[3b, d]

The basic masses of which the burn sludge was composed were extremely rigid. They were sufficiently hard and rigid so that they forcibly bulged the more easily distensible capillaries and postcapillary venules through which they passed. They also forcibly bulged the narrow, strong-walled tips of each arteriole through which they passed. And, what is most significant, while these masses passed through strong-walled arterioles, they themselves did not distort appreciably from their spherical or short rod forms toward spindle shapes. Their lack of plasticity is in sharp contrast to that of the basic masses of the stage III sludge in monkeys with P. knowlesi malaria or the masses in mechanically traumatized dogs. In those two conditions the basic masses are much larger when freely suspended in flowing blood and thus uncompressed than are the basic masses of the burn sludge. However, in the sludge in monkeys with malaria or in traumatized dogs the basic masses are sufficiently soft and plastic so that, as they pass through terminal arterioles, they become much longer and much narrower. Significant features of the basic masses of the burn sludge were that, when uncompressed, they were not as large as those in the aforementioned sludges, but that they had a much higher degree of internal rigidity and were not forcibly distorted in shape as they passed through terminal arterioles. Thus, they presented a maximal resistance to passage through the long, progressively narrow, cone-shaped arterioles, capillaries and venules.

In many dogs the masses have seemed to be about as large as any which could possibly get through maximally dilated terminal arterioles. The limiting conditions to passage are, of course, the sizes of the largest masses which *can* go through, at the time they *do* go through, maximally relaxed, forcibly dilated vessels.

As closely as we can tell at this writing, the masses probably were between 25 and 50 microns in diameter. More precise methods, using filar ocular micrometers in microscopes, are now being used to study the diameters of basic masses.

On a few occasions, a small percentage of the basic masses were larger than the others in the same animal. The largest of these were directly observed to plug terminal arterioles immediately. Obviously, each time this occurred the flow of blood to the tissues, supplied solely by branches of that artery, was immediately cut off.[3d]

2. As time passed, the basic masses of the burn sludge increased in number and they increased in concentration per unit volume of the passing blood. This relative and absolute increase occurred in every set of vessels observed. Usually within half an hour, and certainly in not more than an hour, the greater part of the whole circulating blood was changed to a "homogeneous"[2] sludge (cinema recorded). As noted, this homogeneous sludge consisted for the most part of rigid clumps of red blood cells.

3. Mixed among the basic masses were a few translucent solid objects (cinema recorded). Neither the identity nor the composition of these has been determined. These rather large translucent objects were most easily and clearly seen in small (40 to 80 microns in diameter) veins. They appear to have at least some flat surfaces like crystals and rather sharp edges where such surfaces come together. These masses may be groups of platelets [1b] or precipitated plasma proteins or other substances. They seem not to be masses of agglutinated white cells with which we are familiar from microscopic study of the blood of human patients with leukemia.[2]

B. Visible Changes in Vessel Walls: Concurrently with the progressive increase in the numbers of masses of tightly clumped red cells, white blood cells were observed sticking to the inner surfaces of the walls of the smaller venules, either temporarily, as in the Clarks phase 2 or for much longer periods as in phases 3 and 3 a (cinema recorded). Occasionally, the white blood cells lined venules two layers thick, as in phase 3 b.

Individual white blood cells stuck to the inner surface of the smallest-sized venules obstruct the passage, making it difficult for masses of agglutinated erythrocytes to pass them. Further, whenever the inner surface of the linings of small vessels becomes coated with one or more layers of white blood cells, the coating causes a sharp decrease in the effective internal diameter of the blood vessel. A vessel, for instance, whose real internal diameter is four times the diameter of a white blood cell has an effective internal diameter equal only to that of two white blood cells after its inner surface has been completely coated. This reduction in effective diameter is a powerful factor acting toward reducing the rate of flow of blood through the small vessels.

According to the formula of Poiseuille,[11] which is not completely applicable in this case but is the closest approximation available, the rate of flow through a small vessel is proportional to the fourth power of the diameter of that vessel. Thus, to give a specific example, if all other factors remained equal except that the effective internal diameter of the vessel was decreased to one half its previous value, then the rate of flow of blood would be but one sixteenth its previous rate. This is a most important factor in pathologic physiology but usually is not taken into consideration.

C. Further Visible Changes in the Blood: 1. Three microscopically visible characteristics of the flow of the homogeneously agglutinated blood are direct evidence that there was an increase in the viscosity of

11. (*a*) Poiseuille, J. L. M.: Recherches sur les causes du mouvement du sang dans les vaisseaux capillaires, Mém. Acad. de Sc. Paris **7**:105, 1841. (*b*) Handbook of Chemistry and Physics, ed. 31, edited by C. D. Hodgman, Cleveland, Chemical Rubber Company, 1949, p. 1754.

the fluid material between the masses of red cells: A. As time passed, the clumps of red blood cells were observed to turn over more and more slowly within the moving blood stream. The masses behaved as though they were suspended in syrup or honey or sometimes even as though they were embedded in a rather soft jelly. B. When the stream of agglutinated blood cells within two small venules joined to form a larger stream in the next larger-sized venule, the clumps of red cells from one small stream did not mix readily with the clumps from the other small stream. This continuing separation of the streams was present even though the rates of blood flow became greatly decreased. (Thus, the continuing separation of the streams was not due to the separating forces of rapidly flowing laminar flow systems.) The larger stream frequently consisted, for a considerable distance, of two parallel, viscous, stringy streams visibly separated and moving along within the larger-sized venule. C. In many small venules the blood stops flowing in concentric laminas. Normally fluid blood flows in small veins in concentric layers. Within increasing viscosity of the suspending plasma, the internal layers of such laminar systems stop flowing through the external layers. The whole jelly-like mass then moves forward as a unit. This lack of laminar flow occurred and may be noted in many venules.

Thus, three observed factors indicated that there was an increased viscosity of the blood plasma. These were the progressively increasing inability of a clump to turn over in the suspending fluid, the increasing inability of the two streams to mix homogeneously in a short distance when flowing slowly in a stem venule and the cessation of the laminar flow. All agree with each other, are in the same direction and, we believe, together indicate an increased plasma viscosity (Knisely [2] and Poiseuille [11]).

2. After the burn and after (*a*) the agglutination of the red blood cells, (*b*) the sticking of the white cells to the insides of small veins and (*c*) the increase in the plasma viscosity, there was a sharp reduction in the rates of flow of the passing blood in each and every vessel observed (cinema recorded).

This sharp reduction in the rate of forward flow of blood occurred whether the vessels were maximally relaxed and fully dilated or were but partially dilated (Zweifach and others, and Abell and Page [12]).

The reduction in rate of flow is, we feel, a most significant feature in the pathologic physiology which followed after the blood had become

12. Zweifach, B. W.; Lee, R. E.; Hyman, C., and Chambers, R.: Omental Circulation in Morphinized Dogs Subjected to Graded Hemorrhage, Ann. Surg. **120**:232-251 (Aug.) 1944. Abell, R. G., and Page, I. H.: A Study of the Smaller Blood Vessels in Burned Dogs and Cats, Surg., Gynec. & Obst. **77**:348-353 (Oct.) 1943.

agglutinated. By determining the length of an arbitrarily chosen segment of a venule of approximately 100 microns internal diameter and observing by means of a stop watch the time it took an easily visible clump of red cells to pass through that vessel segment, it was possible to ascertain roughly the rate of flow of the tightly agglutinated masses of burned dog blood sludge. By this method, it was found that the linear rate of flow in the omental vessels of one burned dog had diminished to one third its preburn value by the end of the first half hour after burn.

In one of the rabbits observed a similar decrease soon after the burning was followed by a return to a nearly normal rate of flow at the end of two hours, only to be followed again by a progressive slowing of the blood flow to about one half the normal rate during the next continuous six hours.

Three factors are known to contribute to the forcible reduction in the rate of blood flow through the peripheral tissues following the burn: (*a*) The rigid, basic masses forcibly resist their own passage through the long, progressively narrow, terminal arterioles, the capillaries and the postcapillary venules. (*b*) The white blood cells stuck on the inner surfaces of small venules partially obstruct the venule, and they forcibly decrease the effective internal diameter of the vessel. (*c*) The increase in the viscosity of the plasma certainly also contributes, but to an unknown degree, to the forcible reduction in the rate of flow of blood through the small vessels.

3. As the rates of blood flow slowed down, "charge aggregates," consisting of masses of agglutinated basics, could be seen forming and breaking up in passing venule blood (cinema recorded). These charge aggregates varied in size and in apparent internal cohesiveness. None of them was very rigid. Such charge aggregates in arteries could be seen breaking up into basic masses as they passed into progressively narrower vessels. The aggregates squeezed out into sausage shapes and fell apart into their component basics. Basic masses then passed in single file through the smallest vessels.

D. Changes in the Vessels and Blood Which Occurred After the Blood Stream Had Been Forcibly Slowed Down: A variety of pathologic responses followed the slowing down of the blood stream. As time went on, each factor acted progressively toward stopping the circulation of the blood.

The visible responses may be listed as: (1) slowing of the blood stream to a full stop without apparent leakage of blood fluid from the vessel; (2) weakening, relaxation, bulging and sacculation of the walls of small veins (no aneurysms of small arteries or arterioles were noted); (3) progressive slowing of the blood stream while the walls of small venules leaked the fluid part of the passing blood; (4) appearance of

basic masses of agglutinated red cells outside the vessels, probably but not directly observed, by diapedesis through the vessel wall; (5) occurrence of small hemorrhages which permitted various amounts of the blood with its agglutinated cells to pass through vessel walls into the surrounding tissues; (6) stasis or thrombosis of small vessels, and (7) the plugging of arteriole tips by large-sized basic masses which also acted toward stopping blood flow, as has been previously noted.

The slowing of the blood stream to a full stop frequently occurred without apparent leakage of the fluid part of the blood from the vessel. Sometimes after this response the fluid within a segment of vessel passed out through the vessel wall, and sometimes there was no evidence that it did. This finding is in agreement with and may explain some of the data of Fine and others.[13]

The passage of fluid out of the vessel segment could be noted by the following process. As the arterial pressure forced larger and larger numbers of basic masses into the upstream end of the segment, the basic masses within the segment came closer and closer together and no basic mass passed into the small veins capable of draining the segment. Such concentration of masses finally results, of course, in a stasis or thrombosis of the segment.

Over large areas the walls of small veins weakened, relaxed, bulged and sacculated. This is the phase 4 a of vessel wall reaction to injury. Frequently, the walls of such vessels permitted fluid to pass out while blood flowed *through* the segment for rather long periods. Often sufficient fluid passed out through the walls of such vessels so that the peripheral plasma layer of the blood stream (Poiseuille[11] and Krogh[14]) completely disappeared into the surrounding tissues. In this condition the fluid portions of the entering blood must be passing into the surrounding tissues rather rapidly.

As noted, after the sludged blood had been flowing too slowly for a time, and the rates of oxygen supply to endothelium had been inescapably reduced (stagnant anoxia), the walls of postcapillary venules and small venules lost their ability to retain blood colloids. Anoxia of the endothelium is alone sufficient to cause such leakage (Starr,[15] Starling,[16]

13. Fine, J.; Seligman, A. M., and Frank, H. A.: Traumatic Shock: An Experimental Study Including Evidence Against the Capillary Leakage Hypothesis, Ann. Surg. **118**:238-255 (Aug.) 1943.

14. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1929.

15. Starr, I., Jr.: Production of Albuminuria by Renal Vasoconstriction in Animals and Man, J. Exper. Med. **43**:31 (Jan.) 1926.

16. Starling, E. H.: Principles of Human Physiology, ed. 4, Philadelphia, Lea & Febiger, 1926, p. 854.

Landis,[17] Maurer,[18] Warren and Drinker,[19] Drinker [20] and Block [21]). In a variety of unpublished experiments of ours, sufficiently severe anoxia always caused endothelium to leak fluids rapidly. The larger and more rigid the masses of precipitate-coated agglutinated blood cells, the more they resist passage through the peripheral vascular beds and the shorter the period before the vessel walls begin to leak perceptibly.

Frequently, after various small segments of veins had been in stasis or thrombosed, the direction of blood flow in one or more segments of the network of veins draining an area was reversed, and sometimes there were several reversals as first one part of an area and then another was thrombosed. Such a reversible stream may be nearly stationary for several minutes and begin flowing again, though there is usually then but a slow flow rate (cinema recorded).

Sometimes portions of small thrombi were seen to break loose and be carried on down into the general circulation (cinema recorded). Such masses are usually larger than the basic masses and much more rigid than the usual charge aggregates. It would seem probable that these larger, rigid masses, when carried into the general venous circulation, would plug the vessels at the periphery of the lobules of the liver or portions of the lung or other end organs.

Hartman and Romence [22] have summarized the literature and presented experiments of their own on liver necrosis following burns. It seems possible or probable that multiple minute embolization or thrombosis of liver sinusoids by sludge masses could contribute to this necrosis.

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17. Landis, E. M.: Micro-Injection Studies of Capillary Permeability: III. The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to the Plasma Proteins, Am. J. Physiol. **83**:528 (Jan.) 1928.

18. Maurer, F. W.: The Effects of Decreased Blood Oxygen and Increased Blood Carbon Dioxide on the Flow and Composition of Cervical and Cardiac Lymph, Am. J. Physiol. **131**:331 (Dec.) 1940; The Effects of Carbon Monoxide Anoxemia on the Flow and Composition of Cervical Lymph, ibid. **133**:170 (May) 1941; The Effects of Anoxemia Due to Carbon Monoxide and Low Oxygen on Cerebrospinal Fluid Pressure, ibid. **133**:180 (May) 1941.

19. Warren, M. F., and Drinker, C. K.: The Flow of Lymph from the Lungs of the Dog, Am. J. Physiol. **136**:207 (March) 1942.

20. Drinker, C. K.: The Lymphatic System, Stanford University, Calif., Stanford University Press, 1942, pp. 78-84; Pulmonary Edema and Inflammation: An Analysis of Processes Involved in the Formation and Removal of Pulmonary Transudates and Exudates, Harvard University Monographs in Medicine and Public Health, no. 7, Cambridge, Mass., Harvard University Press, 1945.

21. Bloch, I.: Some Theoretical Considerations Concerning the Interchange of Metabolites Between Capillaries and Tissue, Bull. Mathemat. Biophysics **5**:1 (March) 1943; Some Preliminary Considerations Concerning Concentration of Oxygen in Tissue, ibid. **3**:121 (Dec.) 1941.

22. Hartman, F. W., and Romence, H. L.: Liver Necrosis in Burns, Ann. Surg. **118**:402-416 (Sept.) 1943.

After five to six hours following a burn, basic masses of red cells were seen in increasing numbers outside the vessel walls (cinema recorded; Underhill and Kapsinow [23]). Such masses, and red cells from them, showed a distribution roughly parallel to the walls of small venules. Actual rupture of the vessel walls was not observed. Thus, it seems probable that the basic masses were passing out through portions of sacculated venule walls by diapedesis at irregular intervals. If so, the venule walls were at this time in the Clarks phase 5 of pathologic response.

Occasionally, small to moderate hemorrhages occurred along the walls of small venules (phase 5 a of vessel wall weakening). These obviously also permitted various amounts of red blood cells to get outside the vascular system.

Among other things, these observations show that red cells stationary in small thrombi and outside the vascular system, whether by diapedesis or hemorrhage, (*a*) cease transporting oxygen and (*b*) by their absence from the circulating blood must contribute toward the postburn anemia and toward reducing the circulating blood volume.

The Clarks phase 6 of vessel wall disintegration was not observed.

Each time that a small vessel is embolized or thrombosed, the plugging of the vessel acts toward reducing the circulating blood volume and venous return as follows: (*a*) The stranded masses of blood cells which constitute the minute thrombus or embolus no longer circulate. They are lost from the circulating blood. The volume of the circulating blood is decreased by an amount equal to the total volume of the blood cells in the dilated, impacted vessel. The total volume of the impaction is almost always notably greater than that of the plug or plugs which initiated the impaction. (*b*) The blood fluid which leaves the vascular system, whatever the composition of the dissolved solutes, is lost, at least temporarily, from the vascular system. By this amount the circulating blood volume is also still further decreased. (*c*) The impacted masses, whether thrombi or emboli, directly plug one pathway by means of which blood could have passed from the arterial system to the venous system. The summation of these three sets of factors acts directly toward decreasing venous return to the heart.

The exact amount of the decrease in venous return caused at any one time in a subject by these processes obviously depends on the rates at which these minute thromboses and embolizations and their direct sequelae are occurring minus the rates at which blood volume–restoring processes and vessel-reopening processes are operating.

23. Underhill, F. P., and Kapsinow, R.: The Alleged Toxin of Burned Skin, J. Lab. & Clin. Med. **16**:823-830 (May) 1931.

Enormous numbers of these multiple, minute embolizations and thromboses and their direct immediate consequences occur, both in rapid succession and nearly synchronously, all over the bodies of animals in which (after induction of deep anesthesia) severe intravascular agglutination of the circulating blood has been caused by the burning of distinctly localized, limited portions of their bodies.

Animals did not die until after great numbers of small vessels, all over the body, were solidly impacted.

The phenomena described in section D, those observed to follow the forcible slowing down of the blood stream, were observed in detail in untreated animals. The one burned human patient was treated with intravenous injection of sodium chloride solution, dextrose, plasma and whole blood. In response to these, but not reported here in detail, the basic masses of which her burn sludge was composed were partially broken up into smaller masses. Thus, the forcible slowing down of the blood stream, caused by the resistance of the passage of basic masses through terminal arterioles, did not become maximal and cause the death of this human patient. However, at intervals small areas of the bulbar conjunctiva showed minor degrees of the kinds of phenomena reported in section D.

E. The Phagocytosis of Agglutinated Blood Cells from the Blood Stream Following Burn: Because Knisely and others had observed that the coating on the clumped red cells of monkeys with P. knowlesi malaria opsonized the clumps, permitting the phagocytes of spleen and liver to ingest them,[3c, e] a separate series of experiments was done to study the phagocytosis of clumped red cells following burn.

Early and continued phagocytosis of agglutinated red cells was found in the spleen, liver and bone marrow and will be reported in detail in a later paper.[24] (See also Bigelow and others.[24a])

Knisely, Bloch and Warner [3e] have described in great detail some factors which are both necessary and sufficient to cause particles in the circulating blood to be selectively phagocytosed from the passing blood by the stationary phagocytes of the liver.

SUMMARY OF RESULTS

To summarize the findings, we have confirmed previous observations made in the omental, mesenteric, intestinal and bulbar conjunctival vessels of healthy rabbits and dogs under pentobarbital sodium anesthesia:

24. Skinsnes, O., and Brooks, F.: Phagocytosis of Sludged Blood Following Burn, 1944-1945, unpublished data.

24a. Bigelow, W. G.; Heimbecker, R. O., and Harrison, R. C.: Intravascular Agglutination (Sludged Blood), Vascular Stasis and Sedimentation Rate of the Blood in Trauma, Arch. Surg. **59**:667 (Sept.) 1949.

1. The rate of flow of normally circulating blood is so rapid in 60 to 100 micron vessels that at magnifications of × 32 to × 96 individual blood cells cannot be observed.

2. Individual red cells cannot be seen at a magnification of × 48; approximately × 96 is necessary to see individual, moving red cells clearly.

3. There are no sacculations or tortuosities of healthy vessel walls.

4. There is no evidence of plasma leakage through the vessel walls. (As evidence of plasma leakage, we have taken (*a*) the separation of extravascular fat cells previously held tightly together, (*b*) the progressive packing together of red cells as they move along within the closed vessel, (*c*) increasing difficulty in focusing a deeper layer of vessels and/or (*d*) grossly palpable edema of subcutaneous tissue.)

In contrast to these normal findings which were present in each of our animals before it was burned, we observed the following changes after burn:

1. There was intravascular agglutination of red blood cells into distinctly visible, smooth, hard, rigid, basic masses. These clumps are usually first seen in the postcapillary venules. They obviously resist passage through arterioles, capillaries and venules.

2. White blood cells stick to the vessel walls soon after the burn.

3. Increased plasma viscosity is indicated after burn by the progressive slowing of the rates at which clumps of red cells turn over as they flow along, by the loss of "laminar" flow and by the absence of immediate, homogeneous mixing of venous streams as they join.

4. There was a decreased rate of flow to as little as one third the preburn rate. A decreased rate of flow is the most definite and most easily observed change in the circulating blood after burn.

5. Continuation of reduced rates of flow was followed by sacculation and tortuosity of vessels, by transient and permanent multiple small "thromboses" of small arterioles and venules and must have been accompanied with increased anoxia of surrounding tissues as well as of the vascular endothelium.

6. Leakage of fluid out through vessel walls occurred.

7. Red blood cells were present extravascularly without evidence of ruptured vessels.

8. Small hemorrhages also occurred.

9. These changes were also observed in one human patient, but to a sublethal degree, after an accidental burn.

10. Red cells have been seen in the phagocytes of spleen, liver and bone marrow of recently burned animals.

COMMENT

General Background of Problem.—Since the mechanisms of morbid or lethal changes following a burn have been attributed by some to an as yet unknown "toxin" it is worth while to review the general concepts regarding the "toxic" changes following burn before proceeding to our current experimental concept of these mechanisms.

Harkins [1a] gave a "partial list" of twenty "toxins" postulated to be the cause of death in burns.

The early experiments of Vogt [1c] in 1912 indicate some of the general kinds of changes attributed to such "toxins" following burns. Vogt found that in guinea pigs there is a factor present in the blood after burn which is harmful to the animal burned or to a normal animal whose circulatory system is connected to that of the burned animal. He demonstrated, in parabiotic pairs, that (1) the burned guinea pig did not suffer as severe a "toxemia" as when alone (could this be due to a dilution factor?), (2) the unburned guinea pig did not exhibit "toxic" symptoms when separated within twelve hours after burning, (3) both animals died when they were left united and (4) the urine of the unburned partner, when it died, was always sufficiently "toxic" when injected intraperitoneally to kill a white mouse. In cross circulation experiments with dogs, L. R. Dragstedt and others [25] corroborated these results. From Vogt's results, one can deduce the presence of a "factor" in blood or lymph, following burn, which is sufficient to produce death if not diluted and if allowed sufficient time and that this factor, or one of its metabolic derivatives, is apparently excreted in the urine to a degree sufficient to produce "toxic" symptoms when the urine is injected into a third animal. It is significant, in view of our results, that these general characteristics of the postburn "toxin" are essentially characteristics of changes known to be in the circulatory system.

Many investigators have proposed that histamine, "H-substance" or a "histamine-like substance" is the responsible "toxin" in burn. However, the evidence presented is highly contradictory and is, moreover, essentially negative. The major reports on which histamine or histamine-like substances depend for their consideration are briefly noted here in order to show the kinds of approach which have been made to establish a specific, circulating "toxin" in burns.

Robertson and Boyd,[26] using alcoholic extractions of the burned skin of rabbits in 1923, had definite results in their search for a burn "toxin" which seemed to them to be a proteose. However, Underhill and

25. Dragstedt, L. R., and others: Unpublished data, 1944-1945.

26. Robertson, B., and Boyd, G. L.: The Toxemia of Severe Superficial Burns in Children, J. Lab. & Clin. Med. **9**:1-14 (Oct.) 1923.

Kapsinow,[27] using the same extraction technic on the same animal in 1932, were unable to corroborate the findings of Robertson and Boyd; their analyses of the supposed "toxic" fraction revealed that the "toxin" of Robertson and Boyd was merely alcohol incompletely extracted.

In 1927 Harris[28] made alcoholic extracts of normal and burned skin of guinea pigs and human beings and biologically assayed these extracts for their histamine content (method of Best and Dale). He found the burned skin of these animals and human beings to contain "no more and no less of the histamine than did uninjured skin"; further, burn blister fluid contained no more of the substance than blood plasma.

Rosenthal[29] in 1937 demonstrated that the serum of previously burned animals in which the wound had completely healed was able to neutralize the action of histamine. He made no effort, however, to relate these findings to the clinical state of the postburn patient.

Barsoum and Gaddum,[30] using their own method of estimating blood histamine in human beings, demonstrated that the histamine increased and was maintained at a level at least four times the normal in the blood for many days after burns. These results were confirmed by Dekanski[31] in 1945. Barsoum and Gaddum themselves pointed out, however, that there was no correlation between the blood histamine level and the clinical condition of their patients.

L. R. Dragstedt and others[25] have found further evidence that histamine is not present in physiologically or pathologically significant quantities after burn in dogs. Using dogs in which total gastric pouches had been made, they demonstrated a decrease in the volume of gastric juice secreted after burn as compared with the preburn secretion of the same dog. That these burned dogs continued to respond to the injection of histamine by secreting gastric juice in amounts above the preburn normal is further evidence that active histamine was not present in sufficient quantity to play an important role in postburn pathologic physiology.

These extractions, biologic assays, quantitative determinations and immunologic and pharmacologic demonstrations have failed not only to

27. Underhill, F. P.; Kapsinow, R., and Fisk, M. E.: Studies on Mechanism of Water Exchange in Animal Organism: I. The Nature and Effects of Superficial Burns, Am. J. Physiol. **95**:302-314 (Nov.) 1930.

28. Harris, K. E.: Observations upon a Histamine-Like Substance in Skin Extract, Heart **14**:161-176 (Dec. 21) 1927.

29. Rosenthal, S. R.: Histamine and Burn Toxin, Ann. Surg. **106**:257 (Aug.) 1937.

30. Barsoum, G. S., and Gaddum, J. H.: The Effect of Cutaneous Burns on the Blood Histamine, Clin. Sc. **2**:357-361 (Dec.) 1936.

31. Dekanski, J.: The Effect of Cutaneous Burns on Histamine in Mice, J. Physiol. **104**:151-160 (Oct. 15) 1945.

demonstrate the presence of histamine or histamine-like substances in significantly increased amounts after burn but also to show that histamine has any necessary causal connection with the "toxic" symptoms or "shock state" following burns. While these reports provide little or no positive evidence that histamine is the burn "toxin," they do reaffirm Vogt's and Dragstedt's demonstrations of the presence of some circulating or circulatory factor which produces the "toxic" symptoms following burn.

Background of Specific Problem.—There has been considerable evidence presented regarding mechanical changes in the circulating blood following burn although such changes have generally been considered of minor significance. Before the significance of any change in the circulatory system, or any system, can be determined, it is necessary that the healthy normal state of that system be known. Since the recent work of Knisely and others,[32] which has firmly established the mechanical characteristics of healthy normal circulating blood, it is possible to determine whether or not there are abnormal changes in the physical characteristics of the circulating blood following burn. Before one can interpret and determine the pathologic significance of any change in a system, it is equally necessary to know not only the healthy normal state of that system but also its anatomic and physiologic limitations.

When one considers the diameters of arterioles, terminal arterioles, capillaries and sinusoids, postcapillary venules and small veins and the inherent limitations in their ability to dilate, one is abruptly confronted with the fact that there is constantly present a finite bottleneck, even to normally unagglutinated circulating blood (see Knisely and others [2] and "Materials and Methods" in this article).

Plugging of this bottleneck has been previously reported to occur after burns, though it has been rarely thought to be of significance. Fraenkel,[33] Bardeen,[34] Salvioli,[1b] Underhill and Kapsinow [23] and Kabat and Levine [35] have previously reported the presence of capillary "emboli," "thrombi" or "red cell aggregates" in the spleen, liver, kidney, mesenteric vessels and edematous subcutaneous tissue following burns.

Fraenkel in 1889 [33] remarked on the "thrombi" which he observed in the histologic sections of kidney, liver and spleen taken from 4 patients

32. Knisely and others.[2c, d] Knisely and others.[2]

33. Fraenkel, E.: Ueber anatomische Befunde bei acuten Todesfällen nach ausgedehnten Verbrennungen, Deutsche med. Wchnschr. **15**:22-23, 1889.

34. Bardeen, C. R.: A Study of the Visceral Changes in Extensive Superficial Burns, J. Exper. Med. **2**:501-514 (Sept.) 1897; A Review of the Pathology of Superficial Burns, Johns Hopkins Hosp. Rep. **7**:137-179, 1898.

35. Kabat, H., and Levine, M.: Capillary Emboli as a Lethal Factor in Burns, Science **96**:476-477 (Nov. 20) 1942.

who had died of burns; he also noted "hyperemia" of the organs and hemoglobin pigment in the pulp cells of the spleen. Bardeen's similar observations were on histologic sections.

Salvioli [1b] is, as far as we have been able to find, the only previous investigator who attempted to watch the circulating blood in vivo before and after burn. (See also Bigelow and others.[24a]) His methods and findings are, therefore, considered rather extensively here. He used guinea pigs, rabbits, cats and small dogs anesthetized with chloralose. By means of Thoma's apparatus,[36] he observed blood circulating through the mesentery which was spread over the stage of the apparatus. The observed tissue was bathed with plain water maintained at 37 C, although the invention of Ringer's solution had taken place in 1883!

Salvioli's experiments differ from ours in that he directly observed vessels in the burned tissue; we observed blood and vessels anatomically distant from the site of burn.

One to two minutes after exposing the mesentery to moderately hot saline solution (55 C.), he observed that the vein dilated and a previously closed branch of an artery opened and after ten minutes white cells were rolling very slowly along the vessel (vein) walls so that aggregates of 5 to 7 white cells were formed and constantly moved along the blood stream. In the course of the experiment he also observed that the vessel walls became "irregularly wavy" rather than parallel as they had been in the beginning. He believed these irregularities to be due to the settling of blood platelets in special areas of both veins and arteries. In the vein he observed these masses which he called platelets to narrow the lumen and in the artery to occlude the lumen. He found the same situation in other fields where, in addition, he noted that the circulating plugs of platelets were followed by dense masses of red cells. He attributed the formation of these red cell masses to their piling up in the impeded flow behind the platelet plugs. (Zahn [37] noted red cells collect behind plugs of white cells rather than platelets.) After twenty-five to thirty minutes the blood in all the vessels in the burned area had gradually become stationary. In frogs whose mesenteries were exposed to saline solution heated to 40 or 45 C. a similar stasis occurred. However, by puncturing one of the veins in which there was stasis, Salvioli demonstrated that the blood was actually still fluid but composed of plasma containing "red cells in groups of various sizes as they are never seen

36. Thoma, R.: Die experimentell-mathematische Behandlung des Blutkreislaufes, in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenberg, 1927, sec. 5, pt. 4, II., pp. 1103-1260.

37. Zahn, F. W.: Untersuchung über Thrombose, Virchows Arch. f. path. Anat. **62**:81-124, 1875.

in normal blood." When the blood of a dog was defibrinated prior to burning, thrombi were not formed, nor were platelet plugs seen.

Salvioli's eagerness to explain the entire stasis phenomenon which he observed on the basis of platelet plugs alone may be at least partially ascribed to the fact that his teacher, Bizzozero, had just participated in the discovery of the existence of blood platelets. There are, however, noteworthy similarities and differences between his direct observations of the circulating blood in vivo and ours. His observations that white cells stick and roll along injured vessel walls, that vessel walls become "irregularly wavy" after injury (which we of today would call sacculation because the vessel walls bulge widely), that red cells form in masses, that sections of flowing blood gradually become stationary without thrombosis and that the blood after a burn contains groups of red cells of various sizes never seen in normal blood are consistent with our observations.

That all the vessels in an area exposed only to thermal trauma should "thrombose" is not consistent with our observations; it is consistent with changes which we have observed when a tissue is exposed to air and allowed to become relatively dry. It is known today that it is impossible to maintain exposed tissues in physiologic environments while bathing them with plain water.

That Salvioli was not able to produce "thrombi" with heated saline solution applied to blood previously defibrinated seems significant in view of our observations that the red cells after a burn become coated with a substance which is sticky and which might perhaps be fibrinogen.

Underhill and Kapsinow (1930) published still pictures of alterations in the blood in vessels of abdominal fascia subtending burned areas in rabbits. These alterations in their experience were "exceptional." Four hours after burn, they observed the terminal capillaries to be "densely packed with aggregations of red blood cells." In some areas the capillaries appeared dilated "with extrusion of pocket-like projections (sacculations) filled with corpuscles." They noted that in some instances it appeared that "some of these extrusions have broken and the corpuscles have found their way out of the lumen of the vessel." Twenty-four hours after burn they noted that extravascular red cells were more prominent (see our section on "Results") and that the capillaries were further dilated by densely packed red cells. They suggested that the capillary damage thus presented could "further indicate the role played by the capillary in the production of edema." They did not, however, suggest the aggregation of red cells or their dense packing as the initiating factor of such capillary damage.

Kabat and Levine,[35] searching for the cause of early death in burned cats, were able to reproduce the sudden death by the reinjection of

citrated blood heated to 56 to 65 C. As little as 3 to 4 cc. of heated blood was sufficient to produce rapid death. Autogenous plasma, heated similarly, gave similar results when injected. Autopsies revealed only congestion of organs (see Vogt, Fraenkel and Bardeen) and "widespread and numerous capillary protein emboli." They postulated that these emboli could "play a role in the constitutional effects of severe burns" though they never demonstrated such emboli to develop as the result of burning an animal, nor did they demonstrate that the temperature of a burned animal's blood might reach the 56 to 65 C. required to produce the emboli.

There is little doubt, then, that "thrombi," "emboli" or "red cell aggregates," as well as abnormal behavior of white cells, occur in the blood after burn. These constitute known definite changes in the circulatory system in burn-simulating conditions and in experimentally burned animals. In view of the recent work of Knisely and others, who found that blood precipitates as it flows past crushed tissues,[3b] it seemed likely that such "thrombi," "emboli" or "aggregates" could play a significant role in the production of burn shock.

In summary, we were presented with the evidence that the mechanisms involved in the production of burn shock (1) were still unknown; (2) have generally been attributed to a class of substances called "toxins" for which no causal relationship to burn shock or burn anemia has been demonstrated, and (3) have consistently been shown to be correlated with generalized changes in the circulatory system, its vessels and the constituents of the blood.

When one considers the current clinical usages and meanings of the words "toxin," "toxemia" and "toxic state," one realizes that often actually a generalized change is implied and not a specific change brought about by a specific chemical substance acting in a specific way. A "toxin" is a poison to the entire body in this instance and not to any particular part. It seems likely that the mechanism of generalized action of such a "toxin" would have to be through one or more of the generalized systems of the body, nervous and hemolymphatic. Since changes in the circulatory system have been demonstrated to follow burns, it further seems likely that the changes attributed to the effects of a "toxin" and described as "toxemia" or "toxic state" might well be synonymous with changes in the circulatory system and the circulating blood following burn.

Consideration of Results Observed.—Knowing that changes have been demonstrated in the circulatory system and the circulating blood after burns and knowing the normal state of the circulatory system and the circulating blood, we were presented with the problems of demonstrating whether or not the abnormal changes in the circulating blood

following burn are sufficient to cause the clinical picture of burn shock and/or burn "toxemia" and of determining whether or not these abnormal changes are necessarily the causal mechanism of production of these states.

Let us first recall several factors which have been considered to produce "shock" after burns. Blalock [38] and Harkins [39] demonstrated that fluid loss in and near the burned area is an important factor in the development of burn shock. However, Prinzmetal, Bergman and Hechter [40] demonstrated the following facts: 1. Animals mildly burned, in which shock does not develop, exhibit greater local fluid loss than the animals dying from severe burns. 2. Animals may die in shock with insignificant local fluid loss after a severe burn. 3. Animals which survive a severe burn exhibit considerably greater local fluid loss than those which succumb. The authors concluded that after certain types of burns animals may die in shock not due to local fluid loss.

These opposite concepts show that there may be at least two kinds of shock resulting from burn, either of which kind is sufficient to kill the burned animal: one in which there is not sufficient loss of fluid to account for the resulting state of shock, but for which the mechanism is not yet known, and one in which the known part of the mechanism appears to be the loss of fluid locally into the burn site.

Numerous workers have provided evidence to support the theory of the vicious cycle of anoxia in the production of traumatic shock: Fluid loss following trauma is thought by some to lead to hemoconcentration, which in turn leads to slowed rates of flow, which causes anoxia of vascular endothelium leading to progressive loss of fluid generally throughout the body and thereby progressive shock. That the intravascular agglutination of red cells following burn directly causes slowed rates of flow, leakage of fluid through what must be at least partly anoxic walls, hemoconcentration and progressive fluid loss has been observed by us and cinematographically recorded. There is little doubt that, unless reversed, intravascular agglutination of red cells following burns would be sufficient to cause shock by generalized fluid loss.

If intravascular agglutination of red cells occurred sufficiently suddenly and throughout a sufficiently large portion of the total circulation,

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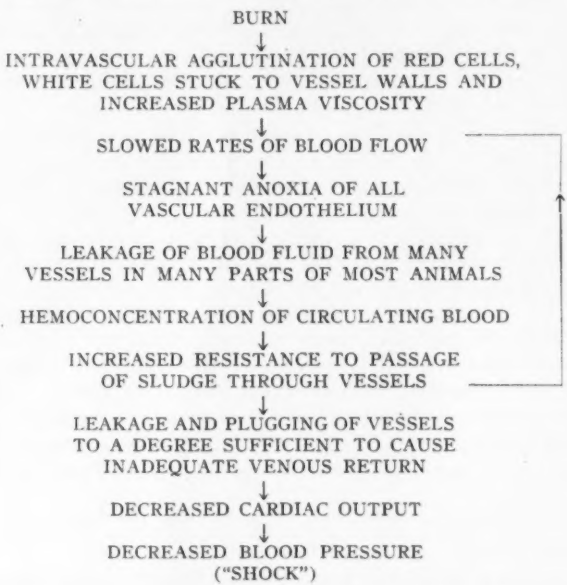
38. Blalock, A.: Experimental Shock: VII. The Importance of the Local Loss of Fluid in the Production of Low Blood Pressure After Burns, Arch. Surg. **22**:610-616 (April) 1931.

39. Harkins, H. N.: Shift of Body Fluids in Severe Burns, Proc. Soc. Exper. Biol. & Med. **31**:994-995 (May) 1934; Experimental Burns: I. The Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns, Arch. Surg. **31**:71-85 (July) 1935.

40. Prinzmetal, M.; Bergman, H. C., and Hechter, O.: A Demonstration of Two Types of Burn Shock, Surgery **16**:906-913 (Dec.) 1944.

the rates of flow would be reduced at such a rapid rate as to cause sudden shock (peripheral failure) in which there would be, grossly, little loss of fluid. However, if the intravascular agglutination of red cells occurred more slowly and more gradually progressed throughout the total circulation, the rates of flow would be reduced gradually, allowing progressive anoxia of all vascular endothelium with progressive loss of fluid throughout the body and the type of shock in which there would be grossly visible fluid loss (edema), present at the burn site and elsewhere, several hours after burn.

A rapid or a slow decrease in the rate of flow of the circulating blood by this sludging process following burn is, therefore, a mechanism sufficient to produce the two types of shock following burn thus far described. The proposed mechanism for the production of the second type of shock, following intravascular agglutination of red blood cells and increased plasma viscosity, resulting from burn, is given graphically in the diagram, which shows the vicious cycle of burn shock.


BURN
INTRAVASCULAR AGGLUTINATION OF RED CELLS, WHITE CELLS STUCK TO VESSEL WALLS AND INCREASED PLASMA VISCOSITY
SLOWED RATES OF BLOOD FLOW
STAGNANT ANOXIA OF ALL VASCULAR ENDOTHELIUM
LEAKAGE OF BLOOD FLUID FROM MANY VESSELS IN MANY PARTS OF MOST ANIMALS
HEMOCONCENTRATION OF CIRCULATING BLOOD
INCREASED RESISTANCE TO PASSAGE OF SLUDGE THROUGH VESSELS
LEAKAGE AND PLUGGING OF VESSELS TO A DEGREE SUFFICIENT TO CAUSE INADEQUATE VENOUS RETURN
DECREASED CARDIAC OUTPUT
DECREASED BLOOD PRESSURE ("SHOCK")

The possibility of one or several "toxins," however, is still not eliminated. It seems entirely possible that some substance or substances released from burned tissue could cause the agglutination of the red cells in the "sludging" process; such a substance might properly be called a

"sludge-initiating toxin." It will not be possible to determine the presence or absence of a specific toxic substance after burn until the sludging process, now known to occur, has been prevented or reversed or until these changes can be definitely attributed to a specific substance. Nor will it be possible to determine how important a role "sludging" of the blood following burn plays in the production of shock until the sludging can be reversed and the presence or absence of shock found possible or impossible without it. Sludging of the blood following burn now seems to be a mechanism sufficient to initiate shock, but whether it is the only mechanism present after burn which is capable of initiating a shock state can be determined only by finding whether or not factors sufficient to produce a shock state occur in the absence of this sludging.

The effects of various therapeutic agents, designed to reverse this vicious process once it has begun or to prevent it from occurring, must now be investigated.

Besides offering a potential mechanism for shock following burn, the changes observed in the circulating blood after burn are of importance for numerous other reasons. One of the first changes noted to occur after burns is the presence of the white cells sticking to venule walls (Salvioli[1b]). Since the sticking of white blood cells has been shown to be one of the first evidences of injury of vascular endothelium,[41] it is thought that this reaction represents the response of vascular endothelium to injury caused either by a circulating "toxin" released from the burned area or possibly by the generalized, stagnant anoxia of vascular endothelium occasioned by the slowed rate of flow of the sludged blood. From our observations to date, however, it is not possible to state which of these factors, toxin or anoxia, causes white cells to stick to endothelium after burn.

Increased plasma viscosity, indicated in our observations by the increasing difficulty with which clumps of red cells turn over as they move along, is difficult to interpret. Since the viscosity of the plasma is dependent chiefly on the state of its protein constituents, it appears that the increase observed must indicate a change or changes in the plasma proteins. It seems likely that the kind of process which causes a sticky coating to form about and agglutinate red cells could also cause other changes in the plasma. That these two changes, formation of a sticky coating and increase in plasma viscosity, result from the same, single or similar multiple processes cannot be stated from available data. Whether the sticky substance, which coats the red cells, represents a loss from the circulating plasma (as indicated possibly by Salvioli) that leaves it more viscous, whether some factor outside the plasma acts on some factors inside the plasma to produce changes in those plasma factors

41. Clark, E. R., and Clark, E. L.[8a] Salvioli.[1b]

which result in the formation of both the "sticky substance" and increased viscosity or whether the factors involved in these changes arise in vessel walls or elsewhere are all basic questions yet to be answered.

There are several reports of alterations in plasma or plasma fractions which lead to shock that may have some bearing on the changes constituting the sludging process which we have observed. Mirsky and Freis [42] reported that the administration of a crude trypsin preparation to rats and rabbits either resulted in rapid death associated with intravascular clotting or caused a "shocklike" syndrome characterized by hepatic and renal damage similar to that observed in burns or the "crush syndrome." Whether or not the sludging of blood following burns can be duplicated by the injection of altered plasma fractions (as suggested by the work of Kabat and Levine [35]), by other single chemicals known to be present after burns (such as histamine), by some substance which is capable of being excreted in the urine (as suggested by Vogt [1c]) or by the injection of proteins and amino acids (as suggested by the work of Mirsky and Freis) has yet to be determined.

Regarding the possible role of such single chemicals, it is noteworthy that Root and Mann [43] produced shock by means of trauma caused by rubber band tourniquet in rats and reported congestion of the capillaries by direct observation. Neither the shock state nor the congestion of capillaries, they concluded, could be ascribed to histamine applied locally or injected intravenously.

The presence of (1) extravascular red cells, (2) red cells trapped in transient and permanent, multiple, small "thrombi" and (3) red cells in phagocytes after burn indicates three methods by which red cells are lost to the circulation. The loss of such cells not only contributes to an inefficient oxygen supply to tissues but must be at least a contributing factor to the production of the early anemia of burns (Harkins,[1a] pp. 76-78). Moore and Cope,[44] by both dye and radioactive iron-tagged red cell methods, have demonstrated that the loss of red cell mass in human beings may be as high as 200 cc. per day during the first four days after burn. They also reported that urobilinogen is excreted in urine and feces in increased amounts, especially in this early period. The increased urobilinogen output tends to indicate that phagocytosis is a significant

42. Mirsky, I., and Freis, E. D.: Renal and Hepatic Injury in Trypsin "Shock," Proc. Soc. Exper. Biol. & Med. **57**:278-279 (Nov.) 1944.

43. Root, G. T., and Mann, F. C.: An Experimental Study of Shock with Special Reference to the Capillary Bed, Surgery **12**:861 (Dec.) 1942.

44. Moore, F. D., and Cope, O., in Minutes of the Meeting of the Sub-Committee on Infected Wounds and Burns, Office of Scientific Research and Development, Washington, D. C., June 2, 1945.

mechanism in the production of the early anemia of burns. Our finding [24] that such phagocytosis occurs early after burn is consistent with this concept of the production of the early anemia of burns.

CONCLUSIONS

A. There are definite physical alterations in the circulating blood in vivo after burn.

1. There is intravascular agglutination of red blood cells into distinctly visible, smooth, hard, rigid, basic masses. These clumps are usually first seen in the postcapillary venules. They obviously resist passage through arterioles, capillaries and venules.

2. White blood cells stick to the vessel walls soon after the burn.

3. Increased plasma viscosity is indicated after burn by the progressive slowing of the rates at which clumps of red cells turn over as they flow along, by the loss of "laminar" flow and by the absence of immediate, homogeneous mixing of venous streams as they join.

4. There is a decreased rate of flow to as little as one third the preburn rate. A decreased rate of flow is the most definite and most easily observed change in the circulating blood after burn.

5. Continuation of reduced rates of flow is followed by sacculation and tortuosity of vessels and transient and permanent multiple small "thromboses" of small arterioles and venules, and it must be accompanied with increased anoxia of surrounding tissues as well as of the vascular endothelium.

6. Leakage of fluid out through vessel walls occurs.

7. Red blood cells are present extravascularly, without direct observation of ruptured vessels.

8. Small hemorrhages also occur.

9. These changes were also observed in one human patient, but to a sublethal degree, after an accidental burn.

10. Red cells have been seen in the phagocytes of spleen, liver and bone marrow of recently burned animals.

B. The significance and implications of these changes are discussed:

1. Mechanisms by which these sludging changes following burn may lead to shock are indicated.

2. We have no evidence to support the hypothesis that histamine is the "toxin" of burn shock; the evidence presented does not rule out the possibility that some "toxin" exists but strongly indicates that physical changes in the circulating blood may be synonymous with what has previously been called "toxic effect."

3. The extravascular (diapedesis and hemorrhage), intravascular (in "thrombi") and phagocytic loss of red cells from the circulating blood which accompanies the sludging changes following burn may be important factors in postburn anemia.

4. The chemical and/or immunologic factors involved in the initiation of the sludging process and in the laying down of the sticky coating on red cells after burn have yet to be determined. Whether this process is reversible, and the nature of such reversing agents, has yet to be determined.

On the basis of our present knowledge, this sludging process must now be vigorously investigated before one can determine a reasonable and adequate treatment for burned human beings.

POSTOPERATIVE ALTERATIONS IN THE COAGULATION MECHANISM OF THE BLOOD

Observations on Circulating Thromboplastin

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ENDOTHELIAL injury and circulatory stasis occurring in association with operation and the postoperative state are obvious causes of postoperative venous thrombosis. Hewson,[1] however, in 1771 showed that stasis per se will not necessarily cause thrombosis. Furthermore endothelial injury involving any but the smaller veins is rare during a surgical procedure. Many have therefore turned their attention to searching for postoperative alterations in the blood itself which might cause it to be more readily coagulable. The modern wide use of anticoagulants to prevent the occurrence or the extension of venous thrombosis gives added meaning to an attempt to define any hypercoagulability which may exist. Presented in this report are the results of certain studies relative to such an attempt.

Figure 1 presents a graphic summary of the coagulation mechanism in the light of our present knowledge. Any diagram of this complex and controversial mechanism leads to oversimplification and, perhaps, to further controversy. For purposes of experimentation and discussion, however, such a skeleton framework is necessary. Figure 1 is to be regarded as this and no more. The factors listed on the first row are present in normal plasma. Substances listed below this line are intermediary or final products of the coagulation process.

In considering the importance of the various factors listed in causing coagulation it is convenient to divide them into two groups:

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Hewson, W.: Works, edited by George Gulliver, London, Sydenham Society, 1846.

(1) those indicated in heavy lettering which are necessary for fibrin formation (calcium ion, prothrombin, platelets, thromboplastinogen, fibrinogen, thromboplastin and thrombin) and (2) those indicated in less heavy letters without which fibrin formation may proceed but which affect the speed and amount of its production (plasma and serum prothrombin accelerators, antithrombin or heparin co-factor, anticephalin and tryptase). There exists in addition a third group of factors which under normal conditions do not participate in the coagulation process but which, in unusual circumstances, may find their way into the blood stream. These may be endogenous (heparin in anaphylactic shock or thrombocytopen in thrombocytopenic purpura) or exogenous e. g., dicumarol® (3,3'-methylene-bis-[4-hydroxycoumarin]) heparin, salicylates and others, given in the form of medicaments.

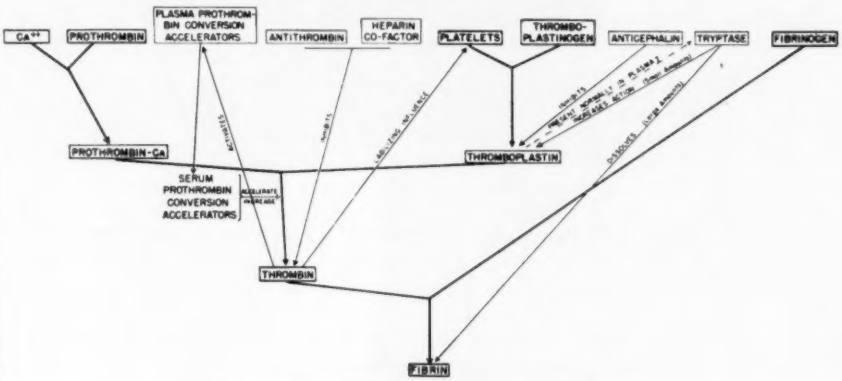

Fig. 1.—Graphic summary of coagulation mechanism.

In the present work a summary is made of past and current opinion on alterations during the postoperative state of the blood levels of factors from the first two groups. After this the results of some experiments of our own are presented.

REVIEW OF THE LITERATURE

Coagulation Time.—Several workers [2] have shown an increased coagulability of the blood as measured by the coagulation time after

2. Cannon, W. B.: The Wisdom of the Body, New York, W. W. Norton & Company, 1932, p. 41. Gray, H., and Lunt, L. K.: Factors Affecting the Coagulation Time of the Blood: V. The Effects of Hemorrhage Before and After Exclusion of the Abdominal Circulation, Adrenals or Intestines, Am. J. Physiol. **34**:332-351, 1914. McClintock, J. T., and Magers, E.: Coagulation Time Fol-

severe hemorrhage in animals, and Cannon [3] showed that adrenalin secretion or administration produced the same effect in cats. Bergquist [4] found a sharp fall in coagulation time in human beings in the early postoperative period and a return to normal in twenty-four to forty-eight hours. Other evidence for alteration in the coagulation time in postoperative patients has been equivocal. This has been due to the unreliability of methods for measuring the coagulation time on whole blood.[5]

Calcium Ion.—The amount of calcium ion necessary for coagulation is less than the minimum amount which can be present in the blood stream and be compatible with life,[6] and conditions which are associated with a high blood calcium level do not reveal a tendency toward thrombosis. No observer to our knowledge has presented data to show that a change in the level of blood calcium can alter the coagulability of the blood. Considerable evidence to the contrary exists.[7]

Prothrombin.—Alterations in the prothrombin concentration of the blood in the postoperative period have been studied and conflicting evidence obtained. No change was observed by Borgstrom [8] or by Allen and Livingstone [9] in patients other than those with obstructive jaundice.

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lowing Hemorrhage After Splenectomy, Proc. Soc. Exper. Biol. & Med. **24**:203-204, 1926. Quick, A. J.: Blood: Annual Review of Physiology **6**:295, 1944. Shafiroff, B. G. P.; Doubilet, H.; Siffert, R., and Co Tui: Effect of Hemorrhage on Normal and Hypocoagulable Blood and Lymph, Am. J. Physiol. **138**:753, 1943. Velden, R. v. d.: Blutverlust und Blutgerinnung, Arch. f. exper. Path. u. Pharmakol. **61**:37, 1909.

3. Cannon, W. B., and Gray, H.: Factors Affecting the Coagulation Time of the Blood: II. The Hastening or Retarding of Coagulation by Adrenalin Injections, Am. J. Physiol. **34**:232-250, 1914.

4. Bergquist, G.: Changes in Blood in Connection with Thromboembolism, Acta chir. Scandinav. (supp. 101) **92**:1-132, 1945.

5. Quick, A. J.; Honorato, R., and Stefanini, M.: The Value and Limitations of the Coagulation Time in the Studies of the Hemorrhagic Diseases, Blood **3**:1120, 1948. Borgstrom.[8]

6. Howell, W. H.: Textbook of Physiology, edited by J. F. Fulton, Philadelphia, W. B. Saunders Company, 1949, p. 545.

7. Addis, T.: The Effect of Administration of Calcium Salts and of Citric Acid on the Calcium Content and the Coagulation of the Blood, Quart. J. Med. **2**:149-164, 1909. Ferguson, J. H.: Blood Calcium and Calcium Factor in Blood Coagulation, Physiol. Rev. **16**:640-670, 1936. Simpson, S. and Rasmussen, A. T.: Does Thyroparathyroidectomy in the Dog Affect the Blood Coagulation Time? Quart. J. Exper. Physiol. **10**:145, 1916.

8. Borgstrom, S.: Prothrombin Index After Operation, Acta chir. Scandinav. **89**:68-74, 1943.

9. Allen, J. G., and Livingstone, H.: Postoperative Hypoprothrombinemia and Anesthesia, Arch. Surg. **42**:522-528 (March) 1941.

More recently Fowler [10] has agreed with this. Brambel,[11] however, found an increase from the third to the fifth day using the dilution technic of Link [12] in performing the test. Rhoads,[13] Shapiro and others [14] and Mahoney,[15] on the other hand, found a decrease during the first week. Shapiro found an increase during the second week after operation. Nygaard [16] and Rehn [17] have independently found increases in the prothrombin concentrations during or just prior to embolism.

Prothrombin Conversion Accelerators.—Ware, Guest and Seegers [18] have found that the prothrombin activity as evidenced by the speed of formation of thrombin from prothrombin when calcium and thromboplastin have been added is less when purified prothrombin is used than when plasma prothrombin is the source of the thrombin. The factor present in plasma which is inferred by this observation has been called by them accelerator globulin and is, they believe, the same as factor V, a substance described by Owren [19] as being deficient in a patient who came under his observation. This patient's plasma had a very low prothrombin concentration as determined by Quick's method. It was found, however, that the addition of prothrombin-free plasma to his plasma in vitro restored the prothrombin time of the specimen to normal. Similar but separate substances have been identified in serum after clot formation has begun by Ware and others, by Owren and by

10. Fowler, N. O.; Roehm, S., and Perlman, H.: A Study of Certain Aspects of Blood Coagulation in the Postoperative State in Congestive Heart Failure and in Thrombophlebitis, J. Clin. Investigation **28**:671-678, July, 1949.

11. Brambel, C. E., and Loker, F. F.: Significance of Variations of Prothrombin Activity of Dilute Plasma, Proc. Soc. Exper. Biol. & Med. **53**:218-220, 1943.

12. Campbell, H. A.; Smith, W. K.; Roberts, W. L., and Link, K. P.: Studies on Hemorrhagic Sweet Clover Disease; Bio-Assay of Hemorrhagic Concentrates by Following Prothrombin Level in Plasma of Rabbit Blood, J. Biol. Chem. **138**:1-20, 1941.

13. Rhoads, J. E.: Physiological Factors Regulating the Level of Plasma Prothrombin, Ann. Surg. **112**:568, 1940.

14. Shapiro, S.; Sherwin, B., and Gordimer, H.: Postoperative Thromboembolization; Platelet Count and Prothrombin Time After Surgical Operations; Simple Method for Detecting Reductions and Elevations of Prothrombin Concentration (or Activity) of Blood Plasma, Ann. Surg. **116**:175, 1942.

15. Mahoney, E. B., and Sandrock, R. S.: The Early Recognition of Postoperative Venous Thrombosis: Increased Prothrombin Activity as an Aid to Diagnosis, Bull. New York Acad. Med. **24**:636-650, 1948.

16. Nygaard, K. K.: Coagulability of Blood Plasma, Proc. Staff Meet., Mayo Clin. **7**:544-548, 1932.

17. Rehn, E.: Über die rationelle Thrombosebekämpfung zu einer embolie-freien Chirurgie, Deutsche med. Wchnschr. **72**:18, 1947.

18. Ware, A. G.; Guest, M. M.; and Seegers, W. H.: Plasma Accelerator Factor and Purified Prothrombin Activation, Science **106**:41, 1947.

19. Owren, P. A.: Coagulation of Blood: Investigations on New Clotting Factor, Acta. med. Scandinav., 1947, supp. 194, pp. 1-327.

Alexander and his colleagues.[20] These last have used the appropriate term "prothrombin conversion accelerators" to designate these substances. No reports have been published dealing with alterations of them in postoperative patients.

Antithrombin and Heparin Co-Factor.—A fall in antithrombin titer of the blood was found by Boshamer[21] in 1927 in the early postoperative period and has recently been observed by Kay.[22] The latter worker has observed a further fall in antithrombin values during active thrombosis. Holden and others[23] have recently observed no fall in the amount of heparin co-factor, a substance closely related to, if not identical with, antithrombin, in the plasma in uncomplicated postoperative cases but a marked decrease in patients undergoing intravascular coagulation. A dissenting voice is that of Volkert and Piper,[24] who found no change in heparin co-factor during active thrombosis.

Blood Platelets.—Platelet Count: But for one or two dissenting opinions,[25] a rise above normal of the blood platelets during the postoperative period has been regularly observed.[26] It is agreed that the

20. (*a*) Alexander, B., and de Vries, A.: A Factor in Serum Which Accelerates the Conversion of Prothrombin to Thrombin: III. Its Relationship to the Coagulation Defect of Thrombocytopenic Blood, Blood **4**:747-751, 1949. (*b*) de Vries, A.; Alexander, B., and Goldstein, R.: A Factor in Serum Which Accelerates the Conversion of Prothrombin to Thrombin: I. Its Determination and Some Physiologic and Biochemical Properties, ibid. **4**:247-258, 1949.

21. Boshamer, K.: Untersuchungen zur Entstehung postoperativer Thrombosen, Klin. Wchnschr. **6**:740-742, 1927.

22. Kay, J. H.: Personal communication to the authors.

23. Holden, W. D.; Cole, J. W., and Davis, J. H.: Clinical Studies of Heparin Co-Factor, Surg., Gynec. & Obst. **89**:20-23, 1949.

24. Volkert, M. and Piper, J.: Heparin Content of the Blood in Chronic Thrombosis, Acta chir. Scandinav. **89**:417, 1943.

25. Allen, E. V.: Changes in Blood Following Operation, Arch. Surg. (April) **15**:254-264, 1927. Sulger, E. and Bozsin, T.: Über die postoperative Thrombose und Embolie sowie ihre therapeutische und prophylaktische Behandlung mit Blutegeln, Deutsche Ztschr. f. Chir. **216**:175, 1929.

26. Adams, E.: Postoperative Thrombocytosis, Arch. Int. Med. **73**:329-335 (April) 1944. Brock, R. C.: Postoperative Venous Thromboses and Platelet Count, Lancet **1**:688-690, 1933. Dawbarn, R. Y.; Earlam, F., and Evans, W. H.: Relation of Blood Platelets to Thrombosis After Operation and Parturition, J. Path. & Bact. **31**:833-873, 1928. Evans, W. H.: Blood Changes After Splenectomy in Splenic Anemia, Purpura Hemorrhagica and Acholuric Jaundice, with Special Reference to Platelets and Coagulation, J. Path. & Bact. **31**:815-832, 1928; Discussion on Postoperative Thrombosis, Proc. Roy. Soc. Med. **22**:11-28, 1929. Hueck, H.: Ueber Untersuchungen der Eiweisskörper des Blutes, sowie Blutplättchen-Zählungen, besonders nach Operationen, Deutsche. Med. Wchnschr. **51**:1869-1870, 1925. König, W.: Experimentelle Untersuchungen über die Entstehung der Thrombose: Ein Beitrag zur Lehre von den Blutplättchen, Arch. f. klin. Chir. **171**:447-502, 1932. Lambert, O., and Driessens, J.: Les modifications

(Footnote continued on next page)

rise begins between the fourth and the eighth day and persists until the twelfth to the sixteenth day. Fewer observers have found a fall in platelets in the first three or four days postoperatively, but this observation has been nevertheless consistent.

Platelet agglutinability, the "stickiness" of platelets, has been studied by one observer, Wright,[27] who found that during the height of the platelet tide in the postoperative period platelets tended to stick to themselves and to rough surfaces more readily than at times when the count was normal.

Anticephalin and Plasma Tryptase.—In so far as we can determine, no observations have been made on either anticephalin or plasma tryptase in the postoperative state.

Free Thromboplastin.—Tests for the detection of free thromboplastin have been indirect in nature. They have consisted of determination of the prothrombin time as carried out by the Howell [28] method and used by Bancroft and others,[29] the heparin tolerance test of de Takats [30] and the heparin resistance test of Waugh and Ruddick.[31] Results obtained by these methods have tended to show an increased coagulability, presumably due to an excess of free thromboplastin in certain patients in whom thrombosis later developed. The lack of specificity of the tests is obvious, since the results may be influenced by factors other than free thromboplastin. Alterations in the prothrombin activity, in the platelet count, in the concentration of heparin co-factor and in that of antithrombin are uncontrolled factors. The serum prothrom-

humorales postopératoires, J. internat. chir. **2**:223-265, 1937. Normann, E.: Wie verhalten sich die Thrombocyten nach operativ behandelten Krankheitsfällen und bei der Entstehung postoperativer Thrombose? Deutsche Ztschr. f. Chir. **212**: 166-178, 1928. Olef, I.: Differential Platelet Count: Its Clinical Significance, Arch. Int. Med. **57**:1163-1185 (June) 1936. Potts, W. J., and Pearl, E.: Study of Platelet Count and Coagulation Time of Plasma and Whole Blood Following Operation, Surg., Gynec. & Obst. **73**:492-494, 1941. Rosenthal, N.: Clinical and Hematologic Studies on Banti's Disease: Blood Platelet Factor with Reference to Splenectomy, J. A. M. A. **84**:1887-1891 (June 20) 1925. Windfeld, P.: Beiträge zur Kenntnis der postoperativen Blutveränderungen, Acta chir. Scandinav. (supp. 25) **70**:1, 1933. Zucker, M. B.: Platelet Agglutination and Vasoconstriction as Factors in Spontaneous Hemostasis in Normal Thrombocytopenic, Heparinized and Hypoprothrombinemic Rats, Am. J. Physiol. **148**:275, 1947. Allen; Sulger and Bozsin.[25]

27. Wright, H. P.: Changes in Adhesiveness of Blood Platelets Following Parturition and Surgical Operations, J. Path. & Bact. **54**:461, 1942.

28. Howell, W. H.: Prothrombin, Am. J. Physiol. **35**:474-482, 1914.

29. Bancroft, F. W.; Stanley-Brown, M., and Quick, A. J.: Postoperative Thrombosis and Embolism, Am. J. Surg. **28**:648-668, 1935.

30. de Takats, G.: Heparin Tolerance: Test of Clotting Mechanism, Surg., Gynec. & Obst. **77**:31-39, 1943.

31. Waugh, T. R., and Ruddick, D. W.: Studies on Increased Coagulability of Blood, Canad. M. A. J. **51**:11, 1944.

bin or prothrombin consumption test [32] which is not complicated by the use of heparin is perhaps a better one. Quick felt that the amount of plasma prothrombin consumed during the coagulation process as measured by the residual prothrombin in the serum was more dependdent on available thromboplastin than on other factors. No work has been found which reports observations on this test in the postoperative state.

Fibrinogen.—Heusser [33] and Allen [35] showed increases in plasma fibrinogen between the fourth and twelfth days after operation. An increase in plasma fibrinogen has been shown to be a response of the body to various states, such as infections and intoxications, by Ham [34] and by Ritter.[35] Cummine and Lyons [36] reported the presence of fibrinogen B, an intermediary product of the reaction between fibrinogen and thrombin, not normally present in the blood, in conditions in which tissue necrosis is present.

TABLE I.—*Types of Operation*

Subtotal gastrectomy	8
Lobectomy	4
Colectomy or colotomy	3
Exploratory laparotomy	3
Closure colostomy	2
Appendectomy	2
Exploratory thoracotomy	2
Resection rectum	1
Saphenous vein ligation	1
Repair of diaphragmatic hernia	1
Excision of popliteal aneurysm	1
Dorsal sympathectomy	1
Vagotomy with gastroenterostomy	1
Repair of gastroduodenocolic fistula	1
Lumbar sympathectomy	1
Total	32

EXPERIMENTAL WORK

We chose to investigate at first alterations in all the necessary building blocks of fibrin except calcium ion, namely, blood platelets, prothrombin, fibrinogen and thromboplastin.

32. Quick, A. J.: Studies on Enigma of Hemostatic Dysfunction of Hemophilia, Am. J. M. Sc. **214**:272-280, 1947.

33. Heusser, H.: Postoperative Blutveränderungen und Ihre Bedeutung für die Entstehung der Thrombose, Deutsche Ztschr. f. Chir. **210**:132-183, 1928.

34. Ham, T. H., and Curtis, F. C.: Plasma Fibrinogen Response in Man: Influence of the Nutritional State, Induced Hyperpyrexia, Infectious Disease and Liver Damage. Medicine **17**:413-445, 1938.

35. Ritter, A.: Ueber die Bedeutung des Endothels für die Entstehung der Venenthrombose, Jena, Fischer, 1926; cited by Silberberg, M.: Causes and Mechanism of Thrombosis, Physiol. Rev. **18**:197, 1938.

36. Cummine, H. G., and Lyons, R. N.: A Study in Intravascular Thrombosis with Some New Conceptions of the Mechanism of Coagulation, Brit. J. Surg. **35**:337-363, 1948.

Studies were made by selecting patients who were to undergo surgical operations. Blood was drawn on at least three different preoperative days and at intervals during the postoperative course not greater than three days in length for periods up to fourteen days. The operations were of varying magnitude and accompanied with varying amounts of blood replacement. A list of the surgical procedures appears in the table. In no patient did postoperative venous thrombosis develop.

METHODS

Prothrombin.—Whole Plasma: The prothrombin activity of whole plasma was determined by the Quick one stage technic [37] using rabbit brain for thromboplastin. Difco bacto-thromboplastin with a mean prothrombin time for normal plasma of 14.3 seconds was used.

Dilute Plasma: The prothrombin activity of dilute plasma was determined by mixing 0.1 cc. of whole plasma with 0.7 cc. of 0.85 per cent solution of sodium chloride giving a solution containing 12.5 per cent plasma. One tenth of a cubic centimeter of this dilute plasma was used for the determination.

The results of both tests, which were read in seconds, were converted to per cent of normal by the use of a previously prepared dilution curve made from various dilutions of normal plasma in 0.85 per cent solution of sodium chloride.

Platelets.—The blood platelets were counted by the direct counting chamber method using capillary blood diluted two hundred times with a solution containing 20 Gm. of sucrose, 5 Gm. of sodium citrate, and 0.1 Gm. of brilliant cresyl blue to 250 cc. of water. This was modified after Rees and Ecker's [38] method in that sucrose was used instead of formaldehyde.

Fibrinogen.—Fibrinogen was determined by isolation of fibrin formed when diluted plasma (1:25) was recalcified. The fibrin was dissolved in 1 per cent sodium hydroxide. An aliquot of this was used for the determination of nitrogen by direct nesslerization.

Plasma Thromboplastin.—1. Heparin Resistance: The Silverman modification [39] of the Waugh-Ruddick Test for heparin resistance was used. This is an in vitro test in which 0.1 cc. of oxalated plasma is added to series of eight tubes, each of which contains 0.2 cc. of 0.01 molar calcium chloride and 0.1 cc. of a solution containing amounts of heparin varying in 1/50 units from 0 to 7/50 units in a 37.5 C. water bath. The tubes were examined for clot formation at half minute intervals. The blood was centrifuged fifteen minutes at 1,000 revolutions per minute. For consistent results it is necessary to standardize the speed and duration of centrifuging as alterations result in large variations in the time required for clot formation. When blood was centrifuged at 3,000 revolutions per minute,

37. Quick, A. J.: Determination of Prothrombin, Proc. Soc. Exper. Biol. & Med. **42**:788-789, 1939.

38. Rees, H. M., and Ecker, E. E.: An Improved Method of Counting Blood Platelets, J. A. M. A. **80**:621-622 (March 3) 1923.

39. Silverman, S. B.: Modification of Waugh-Ruddick Test for Increased Coagulability of Blood and Its Application to Study of Postoperative Cases, Blood **3**:147, 1948.

the clotting time of all tubes was greatly prolonged. This change for a given person can be correlated with the plasma platelet count. Since variations in the test were consistent in all tubes but most pronounced in the eighth tube containing the largest amount of heparin, results are expressed in the minutes necessary for coagulation to occur in tube 8 only.

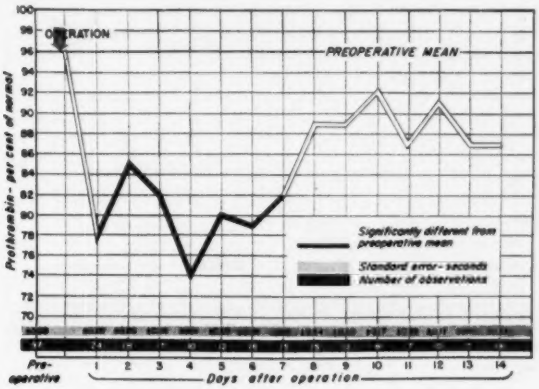

Fig. 2.—Plasma prothrombin activity, whole plasma.

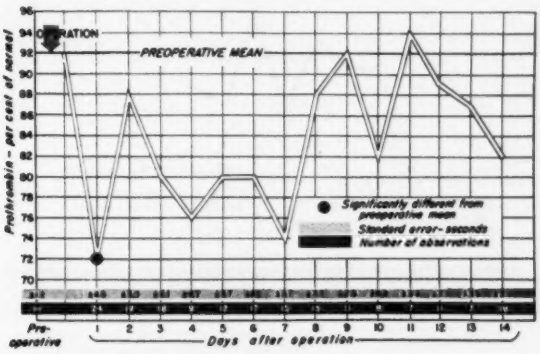

Fig. 3.—Plasma prothrombin activity, diluted plasma.

2. Serum Prothrombin (Prothrombin Conversion): The method used was that of Quick [82] with minor modifications. Blood was drawn by careful venipuncture without trauma and allowed to clot in silicone-coated tubes in a water bath at 37.5 C. One hour after a solid clot had formed, the blood was centrifuged for fifteen minutes at 1,000 revolutions per minute and replaced in the water bath.

For the determination of serum prothrombin, 0.1 cc. of thromboplastin (Difco) and 0.1 cc. of fibrinogen (Armour Laboratories, bovine fraction I, 150 mg. per hundred cubic centimeters in 0.85 per cent sodium chloride) were placed in a clotting tube in the water bath. At the end of two minutes, 0.1 cc. of serum was added and a stop watch was started. The time required for the formation of a fibrin film

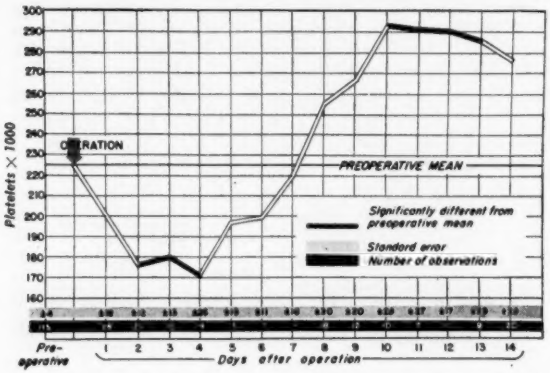

Fig. 4.—Blood platelets.

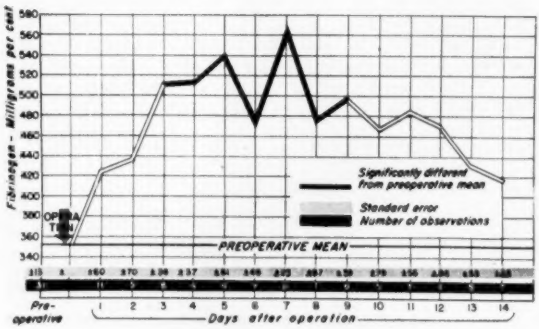

Fig. 5.—Fibrinogen concentration.

was measured. Duplicate determinations were made which checked usually within 0.2 seconds. The determinations were repeated three hours after clot formation. When the blood was allowed to clot in silicone-coated tubes, the results on normal controls and on the preoperative days were consistent. When the blood clotted in glass tubes, we were unable to obtain consistent results from day to day on the same person. Results were expressed in per cent of normal as calculated from the plasma dilution curve.

RESULTS

The results are shown on the accompanying graphs.

Prothrombin.—1. A slight but significant fall in the prothrombin activity of whole plasma from the first to the seventh postoperative

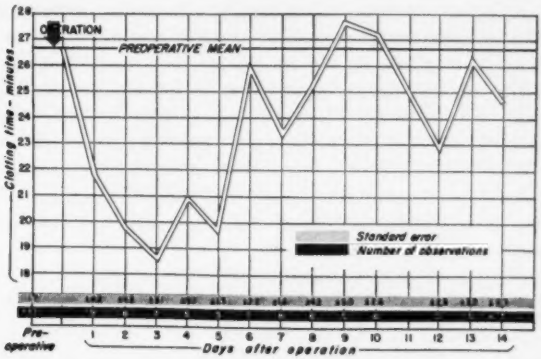

Fig. 6.—Heparin resistance.

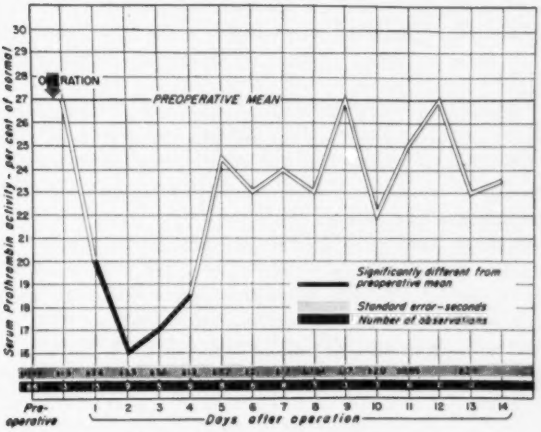

Fig. 7.—Serum prothrombin activity.

day was observed (fig. 2). 2. A less definite fall in activity was found in diluted plasma, that on the first day being the only one statistically significant (fig. 3).

Platelets.—An early fall in platelets was observed which was maximal and significant on the second, third and fourth days. A late rise was observed which was maximal and significant on the tenth, eleventh, twelfth and thirteenth days (fig. 4).

Fibrinogen.—A rise in plasma fibrinogen concentration was observed which was significantly above the preoperative mean between the third and ninth postoperative days inclusive (fig. 5).

Plasma Thromboplastin.—1. By Heparin Resistance Test: A fall in the clotting time of plasma in the presence of heparin (an increased resistance) was observed which was maximal between the second to fifth days (fig. 6). Because of a great variability in our preoperative and normal levels, however, this fact was not statistically significant.

2. By Serum Prothrombin Test: A significant decrease in serum prothrombin was observed between the first and fourth days inclusive (fig. 7).

COMMENT

The fall in the plasma prothrombin in the early postoperative period confirms the work of Rhoads, Mahoney and Shapiro. Its cause is obscure. That it may be due to anesthesia or to losses of prothrombin by hemorrhage which are not replaced by prothrombin-poor bank blood seems unlikely since we have not observed the change in a patient receiving anesthesia for a joint manipulation or in one bleeding massively from a duodenal ulcer who received 1,500 cc. of blood by transfusion. Transient injury to the liver during the surgical ordeal is possible.

The cause of the early fall and the later rise of platelets has been the subject of speculation. Is the fall due to utilization of platelets in the arterioles and venules of the operative field,[40] to destruction in the spleen or to a depressant action on the bone marrow brought about by operation possibly through the agency of a factor emitted by the spleen which has been stimulated by hemorrhage? Is the late rise due to a reactive thrombocytosis on the part of the bone marrow which attempts to repair the early thrombocytopenia or to its attempt to overcome an excess of the hypothetic splenic factor? Much work is necessary to examine these points.

The rise in fibrinogen in the early postoperative period is probably a manifestation of the fibrinogen response as a nonspecific reaction of the body to trauma, toxic states or infection, as outlined by Ham. It is debatable whether the fibrinogen rise can play a part in any postoperative hypercoagulability of the blood, since it has been maintained that

40. Zucker, H. D.: Platelet Thrombosis in Human Hemostasis: A Histologic Study of Skin Wounds in Normal and Purpuric Individuals, Blood **4**:631, 1949.

this degree of change can affect only the quality and not the speed of coagulation.[41] In any case the fibrinogen levels observed are not above the high normal range.

An observation of a fall in the serum prothrombin in the early postoperative period must be considered to be suggestive evidence of the presence of circulating free thromboplastin during this time. It is true that the plasma prothrombin during this period is also slightly decreased. Efforts to calculate the amount of prothrombin consumed in clotting by subtracting the serum prothrombin values from those for the plasma prothrombin are, however, fraught with difficulty. The presence of prothrombin conversion accelerators [20b] in the serum makes the concentration of pure prothrombin therein as determined by the one stage (Quick) test seem higher than it actually is.

A decrease of plasma prothrombin activity to a value of 70 per cent is, we believe, insufficient to affect the serum prothrombin as measured by this test. In patients of our series whose plasma prothrombin level was decreased to only 70 per cent, we did not find consistent comparable decreases in serum prothrombin levels.

Another factor in addition to free thromboplastin which tends to affect the amount of prothrombin converted during coagulation is the platelet level (Alexander [20a]). This being so, the fact that platelets are low in the period during which the prothrombin conversion is apparently increased suggests that there is even more free thromboplastin present than the test reveals.

The degree to which plasma antithrombin affected prothrombin conversion in these patients is admittedly unknown and uncontrolled.

The source of the free thromboplastin which is intimated by the findings is a matter of speculation. Tissue juices from the operative field reaching the blood stream through the lymphatic vessels is the most obvious one. The destruction of platelets as evidenced by the early low platelet count, whether it occurs in the spleen or in the capillaries of the operative field, is another.

We are obliged to state that throughout this work we have been conscious of the inadequacies of the methods used due to the lack of ability to isolate, with the exception of fibrinogen and platelets, the substances in question. Furthermore, the results reported have become evident only when analyzed as composite figures. They do not indicate that each postoperative patient can be predicted to show changes superimposable on the curves presented. We consider, however, that they present a picture of tendencies and trends in the postoperative state.

41. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 54.

It is furthermore to be emphasized that since thrombosis did not develop in any of our patients we have as yet no evidence that any of the tests are helpful in predicting that event.

SUMMARY

1. Pertinent observations which have been made by others on the postoperative levels in the blood of elements important in the coagulation process have been reviewed.

2. Studies of the plasma prothrombin, platelets, plasma fibrinogen and plasma thromboplastin have been made.

3. The plasma prothrombin activity decreased in the early postoperative period. The circulating platelets decreased in the early and increased in the late postoperative periods. The plasma fibrinogen was increased above normal from the third to the ninth postoperative days. The heparin resistance and serum prothrombin tests gave suggestive evidence of the presence of circulating thromboplastin in the early postoperative period (first to fifth days).

PROSTATIC CANCER

Further Investigation of Hormonal Relationships

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IN 1941 research in prostatic cancer received great impetus from the discovery by Huggins and his associates [1] that remarkable regression occurred clinically in the primary neoplasm and its metastases after castration or administration of estrogen. These findings were subsequently verified by others.[2] Unfortunately, the gratifying improvement manifested by most patients treated in this manner has since been found to be only temporary, and no actual cures have ever been recorded. Furthermore, postmortem studies on patients in whom no palpable or roentgenologic evidence of local or distant recurrence was evident just before death have shown extensive involvement of the prostate, bones and soft tissues. In all cases in which radical perineal prostatectomy has been done for advanced cancer after preoperative administration of

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Read before the Section on Urology at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 10, 1949.

This work was supported in part by the American Cancer Society's institutional grant to the Johns Hopkins University School of Medicine and in part by a grant from the National Brewing Company.

1. Huggins, C., and Hodges, C. V.: Studies on Prostatic Cancer: I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate, Cancer Research **1**:293, 1941. Huggins, C.; Stevens, R. E., and Hodges, C. V.: Studies on Prostatic Cancer: II. The Effect of Castration on Clinical Patients with Carcinoma of the Prostate, Arch. Surg. **43**:209 (Aug.) 1941. Huggins, C.; Scott, W. W., and Hodges, C. V.: Studies on Prostatic Cancer: III. The Effects of Fever, of Desoxycorticosterone and of Estrogen on Clinical Patients with Metastatic Carcinoma of the Prostate, J. Urol. **46**:997, 1941.

2. Herbst, W. P.: The Effects of Estradiol Dipropionate and Diethylstilbestrol on Malignant Prostatic Tissue, Tr. Am. A. Genito-Urin. Surgeons **35**:195, 1941. Alyea, E. P., and Henderson, A. F.: Carcinoma of the Prostate: Immediate Response to Bilateral Orchidectomy: Clinical and X-Ray Evidence, J. A. M. A. **120**:1099 (Dec. 5) 1942.

estrogen, malignant cells have been readily demonstrated in the surgical specimens.[3] We have thus been forced to conclude that although existing methods of endocrine manipulation have undoubtedly been of real benefit in the majority of patients so far as their symptoms were concerned they have not provided the final answer.

At present the effectiveness of castration or estrogen therapy in disseminated prostatic cancer is measured by certain subjective and objective criteria. Many of these criteria are confusing. For example, serum acid phosphatase levels are normal in approximately 35 per cent of cases of widespread prostatic cancer. Frequently we fail to observe lowering of increased serum acid phosphatase values after castration or administration of estrogen. Increase of a previously normal acid phosphatase value has been observed immediately after castration. Thus, though trends can be demonstrated, unidirectional changes are not consistent. These minority changes may be important.

Initially, when the investigation of hormonal relationships in prostatic cancer was being continued, it seemed appropriate to reconsider the original premise on which recent hormonal management is based. We refer to Huggins' concept that prostatic cancer is an overgrowth of adult prostatic epithelial cells and that adult prostatic epithelial cells undergo atrophy when androgens are reduced by castration or inactivated by estrogen administration. Wide acceptance of the thesis that androgens must be removed, neutralized or destroyed led Huggins and his associates, as well as others, to search for sources of androgen in organs other than the testes and for ways of removing, neutralizing or destroying them.

That the adrenal gland is an extragonadal source of androgens seems clear, both in animals and in man. However, in a study by Huggins and Scott,[4] in which they surgically removed the adrenals in a patient previously castrated for prostatic cancer, the tumor at autopsy was widely disseminated in spite of evidence, based on urinary assays, that body androgens were low. On this evidence they postulated that certain prostatic cancers were independent of androgen.

It appears to us that if continued progress is to be made in the treatment of prostatic cancer, the exact role of androgens in the induction of cancer or the maintenance of cancer growth must be ascertained. If androgen dependence is all-important, other means of eliminating

3. Colston, J. A. C., and Brendler, H.: Endocrine Therapy in Carcinoma of the Prostate: Preparation of Patients for Radical Perineal Prostatectomy, J. A. M. A. **134**:848 (July) 1947.

4. Huggins, C., and Scott, W. W.: Bilateral Adrenalectomy in Prostatic Cancer: Clinical Features and Urinary Excretion of 17-ketosteroids and Estrogen, Ann. Surg. **122**:1031, 1945.

androgens must be explored. If other factors exist, these in turn must be investigated.

We wish to present a report of our clinical findings in a long range study of hormonal relationships in prostatic cancer, in which the effects of androgens were studied. For this purpose we placed under observation a selected group of patients with advanced carcinoma of the prostate. A survey was made of a large number of persons with the disease. Before we embarked on a full scale study project, 3 of these patients, for whom the prognosis was regarded as hopeless, were chosen for preliminary study. After their immediate status had been ascertained by means of rectal palpation, roentgenograms of the bones and serum acid phosphatase assays, each patient received a 200 mg. pellet of testosterone propionate, implanted subscapularly. At regular intervals the patients were seen in the dispensary and reevaluated. Because of the qualitative

TABLE 1.—*Classification Code for Patients with Prostatic Cancer*

1. Rectal findings
   a. Limited to gland proper
   b. Beyond the gland proper
2. Presence of osseous deposits
3. Increase of serum acid phosphatase
4. Histologic classification (of most malignant area)
   a. Well differentiated
   b. Poorly differentiated
   c. Anaplastic
   d. Other (including extension or metastasis to the prostate)
5. Prior treatment (whether diagnosed as cancer or not)
   a. Endocrine (including castration, use of estrogen, etc.)
   b. Surgical
   c. Irradiation
   d. Chemotherapeutic
   e. Other

nature of this preliminary study, no attempt has been made to tabulate or plot the changes which were observed. It is fair to state, however, that 2 of the patients improved considerably within two weeks from a symptomatic standpoint, and in 1 of these there was a palpable decrease in the size of the prostate. The improvement in this patient lasted for about five months, at which time symptoms returned. He was given testosterone linguets,[5] 6.0 mg. daily, and again he improved. The third patient treated by implantation of pellets was somewhat worse during the first week but then returned to his former state, apparently none the worse.

Because of these surprising, but not totally unexpected, observations, a planned program of investigation was begun. By means of a careful screening process (table 1), 3 patients with advanced prostatic cancer

5. Dr. J. Murray Scott, of Ayerst, McKenna & Harrison, Ltd., gave us a generous supply of 6 mg. lingusorbs® of testosterone and Dr. Edward Henderson, of the Schering Corporation, the testosterone propionate used.

were admitted to the hospital and preliminary studies carried out (table 2). In each case biopsy of material from the prostate was done perineally and the histologic diagnosis established. After complete evaluation, the patients were given daily injections of 25 mg. of testosterone propionate in sesame oil. Follow-up studies were made periodically according to plan (table 3). These results were subjected to frequent analysis, and whenever indicated, changes were made in the plan of treatment, as will be seen in the case histories and figures to follow.

TABLE 2.—*Initial Studies*

1.	Basic (complete blood count, urinalysis, nonprotein nitrogen, carbon dioxide, sugar, chlorides, sodium, potassium, calcium, cholesterol, icteric index, proteins, liver function tests, kidney function tests, etc.)
2.	Total neutral 17-ketosteroids
3.	Other hormonal studies (androgen, estrogen and follicle-stimulating hormone)
4.	Serum enzyme studies, including acid and alkaline phosphatase and glucuronidase
5.	Flat roentgenogram and intravenous urogram, roentgenograms of bones
6.	Roentgenogram of chest
7.	Cystoscopy
8.	Touch pictures
9.	Perineal biopsy of prostate
10.	Sternal biopsy
11.	Biopsy of testis

TABLE 3.—*Plan of Action*

1.	Testosterone propionate in sesame oil, 25 mg. daily
2.	Basic weekly laboratory studies
3.	Total neutral 17-ketosteroids twice weekly
4.	Serum enzymes studies daily
5.	Roentgenograms of bones every 2 weeks
6.	Cystoscopy as indicated
7.	Touch pictures weekly
8.	Repeat biopsies of prostate, sternum and testis
9.	Other hormonal studies as indicated

REPORT OF CASES

CASE 1.—L. S., a white man aged 65, was admitted to the hospital on Jan. 17, 1949. A diagnosis of metastatic prostatic cancer had been made elsewhere in 1946 and bilateral orchiectomy performed. Shortly thereafter he received high voltage roentgen ray therapy to the pelvis. Estrogen therapy had been initiated after orchiectomy and continued until the patient's admission. These measures had afforded little relief. On his admission, he complained of severe generalized pain, was found to be in an extreme state of inanition and weakness and was almost moribund. The prostate was small and soft, without evidence of nodularity or fixation. Preliminary studies showed marked anemia, hypoproteinemia, a total 17-ketosteroid excretion of 3.0 mg. per day, a serum acid phosphatase level of 27.9 units and a serum alkaline phosphatase of 25.9 units.[6] Multiple roentgenograms of the bones revealed diffuse osteoblastic metastasis. Perineal biopsy of the pros-

6. Acid and alkaline serum phosphatase levels are expressed in King-Armstrong units.

tate revealed a moderately differentiated adenocarcinoma. Sternal biopsy showed extensive involvement of the marrow with prostatic cancer.

On the eleventh day (fig. 1) injections of testosterone, 25 mg. daily, were begun. After the first week there was less pain, with increased appetite and a gain in weight. Periodic rectal examinations disclosed no appreciable change in the prostate. The hemoglobin content rose from 9 to 12 Gm. per hundred cubic centimeters. As expected, the urinary 17-ketosteroids gradually rose. The serum acid phosphatase rose to 82 units by the twentieth day, and a slight transient rise in the alkaline phosphatase also occurred. On the twenty-fifth day the dose of testosterone propionate was increased to 50 mg. per day, and the urinary steroids and serum acid and alkaline phosphatase levels showed further generalized increases. At this time, the patient's general condition was much improved. On the fortieth day administration of testosterone was increased to 100 mg. daily and maintained at this level until the seventieth day, when it was discontinued. Within fourteen days the acid phosphatase had fallen to 22 units. At approximately the hundredth

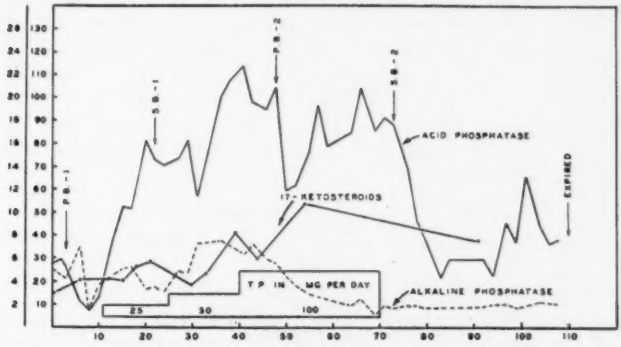

Fig. 1 (case 1).—Ordinates, 17-ketosteroids in milligrams per day (0 to 26); acid and alkaline serum phosphatase (0 to 130 units). Abscissa, days. P. B.-1 and P. B.-2 represent perineal biopsies; S. B.-1 and S. B.-2 represent sternal biopsies.

day his condition changed for the worse, and three days later he died. During this terminal stage the acid phosphatase rose, reaching 67.3 units on one occasion.

Shortly after the dosage of testosterone was increased to 100 mg. daily, we had observed generalized bronzing of the skin, most marked over the head, neck and chest. This resembled addisonian pigmentation and led us to suspect alteration in adrenal function secondary to either metastatic involvement or administration of testosterone. On the seventieth day thrombopenic purpura had developed, thought to be secondary to extreme involvement of the bone marrow with tumor. This condition persisted until death.

Studies of perineal and sternal biopsies made before and after administration of testosterone revealed no striking alterations in the histologic pattern of the tumor. Serial roentgen studies showed no significant changes in the bones.

CASE 2.—W. S., a white man aged 69, was admitted to the hospital on Jan. 20, 1949, complaining of moderately severe urinary frequency, slight diminution in the size and force of the voided stream and a weight loss of 60 pounds (27.2 Kg.) during the previous year. On rectal examination the prostate was enlarged, nodular

and stony hard, with evidence of extension into the left seminal vesicle and periprostatic tissues.

Preliminary studies showed moderate anemia, increased sedimentation rate, with a normal white blood cell count, a urinary 17-ketosteroid level of 4.0 mg. per day and a serum acid phosphatase value of 28.2 units. Roentgenograms of the skeleton revealed generalized osteoblastic metastasis. Perineal biopsy of the prostate disclosed adenocarcinoma. Sternal biopsy showed metastatic carcinoma.

On the twelfth day (fig. 2) injections of testosterone, 25 mg. daily, were begun. This dosage schedule was maintained until the fifty-fifth day when it was increased to 100 mg. daily. On the seventieth day administration of testosterone was discontinued.

During this time, the patient's condition improved somewhat. His appetite increased, and he gained weight. There was no essential change in the rectal findings. The urinary 17-ketosteroids fluctuated widely. The serum acid phos-

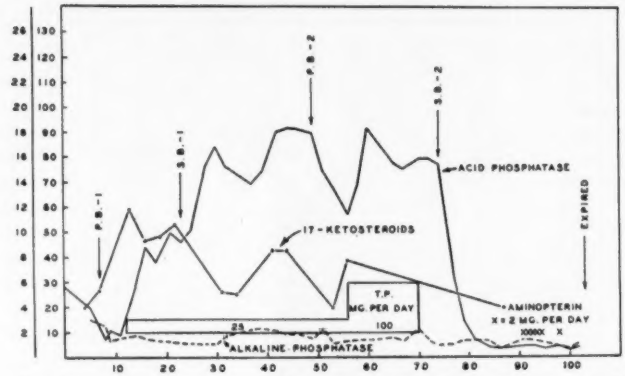

Fig. 2 (case 2).—Ordinates, 17-ketosteroids in milligrams per day (0 to 26); acid and alkaline serum phosphatase (0 to 130 units). Abscissa, days. P. B.-1 and P. B.-2 represent perineal biopsies; S. B.-1 and S. B.-2 represent sternal biopsies.

phatase level rose promptly after testosterone was given and remained increased until shortly after administration of the drug was stopped. In contrast to case 1, the alkaline phosphatase showed little change. Within three weeks after injections of testosterone were discontinued the patient began to suffer a loss of appetite and weight and was confined to bed. However, at no time did he suffer pain in the bones.

From the ninety-first day, in an effort to alter his downhill course, the patient was given daily injections of 2 mg. of aminopterin® (4-aminopteroylglutamic acid), a folic acid antagonist. Five days later hemorrhagic manifestations developed, and the use of the drug was discontinued. On the one hundred and third day he died.

In contrast to case 1, definite histologic changes were noted in prostatic and sternal biopsies. Although the over-all pattern remained the same, the individual cells became swollen, the cytoplasm vacuolated and the nuclei more deeply stained.

On roentgen examination there were no changes in the character or extent of osseous metastasis.

CASE 3.—W. C., a Negro aged 72, was admitted to the hospital on Feb. 5, 1949. During the previous year he had experienced increasing urinary frequency, hesitancy, intermittency and a decrease in the size and force of the voided stream. He had experienced no pain in the bones or other constitutional symptoms. The prostate was found to be markedly enlarged, irregular, nodular and fixed, with extension into both seminal vesicles and lateral pelvic walls. All preliminary studies gave negative results, except for increase of the sedimentation rate to 15 mm. per hour. The urinary 17-ketosteroids were 2.2 mg. per day, serum acid phosphatase 2.7 units and serum alkaline phosphatase 4.3 units. Roentgenograms of the bone failed to show metastasis. Perineal biopsy showed an adenocarcinoma of the prostate. A sternal biopsy gave a negative result.

From the twenty-fifth day (fig. 3) he was given 25 mg. of testosterone propionate daily. This was increased to 100 mg. daily on the forty-seventh day and maintained at this dosage until the sixty-seventh day, when it was stopped. Shortly after the use of testosterone was begun, severe diarrhea developed, which disappeared within one week. Otherwise the patient showed no symptomatic changes during his entire course in the hospital. Repeated rectal examinations disclosed a

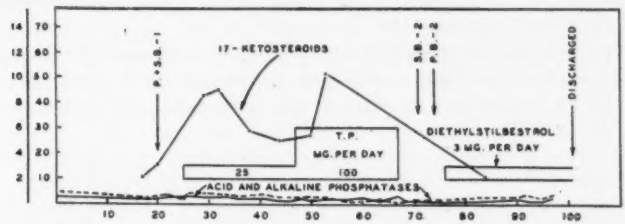

Fig. 3 (case 3).—Ordinates, to 17-ketosteroids in milligrams per day (0 to 26); acid and alkaline serum phosphatase (0 to 130 units). Abscissa, days. P. B.-1 and P. B.-2 represent perineal biopsies; S. B.-1 and S. B.-2 represent sternal biopsies.

definite increase in the size of the prostate to the point where it completely engirdled the rectum.

Urinary steroids rose during administration of testosterone and fell when administration of the drug was stopped. No changes were observed in either acid or alkaline serum phosphatases. No visible bone metastasis developed on serial roentgenograms. A subsequent sternal biopsy showed no evidence of metastatic cancer, but changes were observed in the tissue removed at perineal biopsy which were similar to those observed in case 2.

On the seventy-sixth day because of persistent symptoms of obstruction of the vesical neck, administration of diethylstilbestrol was begun, 1 mg. daily. This was continued throughout the remainder of his stay in the hospital, and on this treatment the urinary symptoms improved.

COMMENT

We have described the clinical and laboratory findings in 3 patients with advanced prostatic cancer who received testosterone propionate in doses varying from 25 to 100 mg. daily for periods up to two months. Two of these 3 patients had extensive secondary involvement of bone, and 1 of these 2 had previously been castrated and had received estrogen.

We were aware that Huggins and Hodges in 1941 had administered androgen in lesser amounts and for shorter periods to 3 patients with metastatic cancer of the prostate who had previously been castrated.

Several points of interest emerge from this study. We were impressed with the general improvement shown by the 2 patients with metastatic prostatic cancer during the period they received testosterone. Pain in the bones was considerably lessened in the patient who complained of this initially and did not develop in either of the other 2.

As evidenced in roentgenograms, metastasis did not develop in the patient initially free from it, nor did remarkable change occur in the 2 patients with metastasis.

Regarding the serum acid phosphatase, it is significant that further increase occurred in the 2 patients with osseous metastasis but not in the one without it. Perhaps occult bony metastasis can be diagnosed by observing the response of the serum acid phosphatase to a short course of androgen injections.

On the basis of these preliminary studies, we believe that further investigation of the role of androgens in prostatic cancer is warranted. It will be recalled that in cases of metastatic cancer of the breast in the female both androgens and estrogens have been used, androgens apparently exerting a more beneficial effect in younger women and estrogens in the older age group. Furthermore, androgens appear to affect osseous metastasis predominantly, whereas estrogens primarily influence the soft tissue metastasis and the primary growth itself.[7] Perhaps an analogous situation exists with reference to prostatic cancer. It is our feeling that reliable information can be obtained only through careful studies which utilize all available technics. In the last analysis, however, the validity of such studies must depend on the manner in which patients are selected. Only then can the relative efficacy of different forms of therapy be properly evaluated.

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CARCINOMA OF THE PROSTATE GLAND; RESULTS OF CONSERVATIVE MANAGEMENT

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THE PRESUMPTIVE diagnosis of carcinoma of the prostate can be made clinically by rectal palpation. McHeffey [1] has shown that urologists can be accurate in the clinical diagnosis of adenofibromatous hyperplasia in 96 per cent of the cases and of carcinoma of the prostate in 88 per cent. Kahler [2] was of the opinion that the perineural lymphatic vessels are involved in practically all cases of prostatic cancer regardless of the size of the tumor or the grade of the malignant disease.

Thompson [3] revealed that the incidence of metastasis varied between 25 and 58 per cent of cases reported.

Greene and Emmett [4] were unable to show lasting benefit from bilateral orchiectomy in a group of 179 patients followed for one year or more. They advocated the procedure only for patients with symptoms secondary to metastasis. Landsteiner and Brown,[5] Barnes,[6]

Read before the Section on Urology at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 10, 1949.

1. McHeffey, G. J.: Carcinoma of the Prostate Gland: Efficacy of Method of Examining Prostatic Tissue Removed by Transurethral Resection to Make a Pathologic Diagnosis of Carcinoma, Proc. Staff Meet., Mayo Clin. **15**:458 (July 17) 1940.

2. Kahler, J. E.: Carcinoma of the Prostate Gland, Proc. Staff Meet., Mayo Clin. **13**:589 (Sept. 14) 1938.

3. Thompson, G. J.: Carcinoma of the Prostate: Its Conservative Surgical Treatment, South. Surgeon **10**:271 (April) 1941.

4. Greene, L. F., and Emmett, J. L.: Further Observations on Treatment of Carcinoma of Prostate by Bilateral Orchectomy, S. Clin. North America **26**:1007 (Aug.) 1946.

5. Landsteiner, E. K., and Brown, H. P.: Observations on Treatment of Carcinoma of the Prostate by Orchiectomy, Am. J. M. Sc. **213**:450 (April) 1947.

6. Barnes, R. W.: Cancer of the Prostate, California Med. **69**:468 (Dec.) 1948.

Huggins,[7] Scott and Benjamin[8] and others describe results with bilateral orchectomy for prostatic cancer.

Jewett,[9] Twinem and Davalos,[10] Colston and Brendler[11] and others believe that preoperative antiandrogenic therapy will render more patients suitable for radical perineal prostatectomy.

Deming[12] expressed the belief that transurethral resection may activate and spread the malignant process, pointing out that the urethral mucosa serves as a natural barrier.

Nesbit and Plumb[13] revealed that the average survival time for 783 patients whose disease was diagnosed and treated prior to the "endocrine era" was 21.2 months (1 patient has lived more than fifteen years). This excellent control series was closely approximated in a survey by Gahagan and Fischman.[14] The findings of both studies indicate that the survival rates for cancer of the prostate are definitely prolonged by either oral antiandrogenic therapy or orchectomy. Dean[15] found that 90 per cent of patients with prostatic malignant disease responded to oral antiandrogenic treatment, while others believe that 80 per cent or less improve.

A review of the literature discloses a paucity of reports concerning groups of patients to whom estrogenic substances have been administered for prolonged periods. Although these substances were used clinically for this condition in 1940, they were not widely employed for treatment of prostatic malignant disease at that time.

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7. Huggins, C.: Prostatic Cancer Treated by Orchiectomy: The Five Year Results, J. A. M. A. **131**:576 (June 15) 1946.

8. Scott, W. W., and Benjamin, J. A.: The Role of Bilateral Orchiectomy in the Treatment of Carcinoma of the Prostate Gland: A Report of 82 Cases, Bull. New York Acad. Med. **21**:307 (June) 1945.

9. Jewett, H. J.: Radical Perineal Prostatectomy, J. Urol. **61**:277 (Feb.) 1949.

10. Twinem, F. P., and Davalos, F.: Radical Surgery in Prostatic Cancer, J. Urol. **61**:575 (March) 1949.

11. Colston, J. A. C., and Brendler, H.: Endocrine Therapy in Carcinoma of the Prostate: Preparation of Patient for Radical Perineal Prostatectomy, J. A. M. A. **134**:848 (July 5) 1947.

12. Deming, C. L.: Present Evaluation of Response of Prostatic Cancer to Hormone Therapy, South. M. J. **40**:328 (April) 1947; The Correlation of Clinical Experience and Heterológous Growth of Human Prostatic Cancer, J. Urol. **61**:281 (Feb.) 1949.

13. Nesbit, R. M., and Plumb, M. D.: Prostatic Carcinoma: A Follow-Up of 795 Patients Treated Prior to the Endocrine Era and a Comparison of Survival Rates Between These and Patients Treated by Endocrine Therapy, Surgery **20**:271 (Aug.) 1946.

14. Gahagan, H. Q., and Fischman, J. L.: Carcinoma of the Prostate: A Statistical Study and Evaluation of Endocrine Therapy, with a Preliminary Report on an Additional Method of Treatment, J. Urol. **61**:587 (March) 1949.

15. Dean, A. L.: Carcinoma of Prostate, Bull. New York Acad. Med. **23**:454 (Aug.) 1947.

Our results with conservative management of patients having carcinoma of the prostate gland have been encouraging. In this study the results with conservative management of 104 consecutive private patients with prostatic cancer who were seen at frequent intervals and treated with oral administration of enteric-coated diethylstilbestrol are reviewed.

In all cases a diagnosis of prostatic malignant disease was confirmed by rectal palpation, roentgenologic survey, chemical determinations or examination of pathologic material or by combinations of these procedures. There were 9 patients for whom the diagnosis had been established by transurethral resection elsewhere.

Evidence of osseous metastasis was disclosed in 39 (37.5 per cent). Most patients had advanced neoplasms when first examined. There were 8 instances (7.7 per cent) in which the diagnosis was not made preoperatively. Among these the histologic picture in 5 was one of high grade malignant disease.

The average age among the group of 104 patients was 68.9 years; 45 (43.7 per cent) were in the eighth or ninth decade.

TREATMENT

Diethylstilbestrol was given orally to all the 104 patients when the diagnosis was first established. Originally the daily dose was 3 mg. or less. For the past five years 5 mg. of the drug has been given once daily. Dosage was increased if symptoms warranted or if metastasis became apparent. We have given up to 50 mg. daily, but the enormous dosages employed by some urologists have not been used. In some instances the dose was reduced to 2 or 3 mg. daily after prolonged therapy.

There were some patients of the 104 among whom evidence of urinary obstruction was lacking or was minimal in degree. These received antiandrogenic hormone medication only.

The drug was used in conjunction with indwelling urethral catheter drainage for a debilitated patient of 86 years having carcinoma of the prostate and complete urinary retention. After a period of three months this man was able to void satisfactorily and no residual urine was found. This experience was subsequently successfully repeated among another 8 patients. The duration of catheter drainage varied but never exceeded three or four months. In 1 patient two weeks was sufficient. Another 6 patients on this regimen were unable to void. All were subsequently relieved by transurethral resection.

We have found this method of managing elderly patients highly satisfactory. Later, if the need for transurethral resection becomes evident, the procedure can be performed on a patient who is in much better health and a better surgical risk than when first seen.

We do not hesitate to carry out transurethral resection when obstructive symptoms warrant it after a trial with an indwelling catheter is considered adequate. A resection was performed in 56 patients (53.8 per cent). A second resection was required because of regrowth of malignant tissue and subsequent urinary difficulty in 13 patients. Five of these needed a third procedure, which made a total of 74 transurethral resections. There was 1 surgical death.

There were 2 patients in whom thrombophlebitis developed postoperatively and another 2 patients who had persistent stress incontinence. We believe that the patients who had stress incontinence were subjected to a resection that was too radical. We subsequently learned not to perform such radical procedures and to depend more on the antiandrogenic hormone treatment.

Tissue in all questionable cases was subjected to frozen section so that antiandrogenic hormone therapy could be started immediately. The drug was given intramuscularly on the day of operation and then orally.

RESULTS

Among the 104 patients in this study 81 are alive, 18 are dead and 5 have not been traced after varying periods (these will be assumed dead).

The average survival period for all patients from the time of treatment until the time of this study was 33.8 months. The average time survived by 81 living patients was 34.7 months. Among these, 13 patients were included who had been treated for less than one year. The average survival time for those treated more than one year (and who are still alive) was 41.1 months. Of the total of 104 patients, 22 (21.2 per cent) had survived more than five years. Of these 22 patients, 16 are still living.

Of 88 patients who lived more than one year, 9 died within five years and 5 (untraced) are probably dead. Sixty-five patients, now living, had been under treatment for less than five years. This would strongly suggest that the number surviving for more than five years will appreciably exceed 21.2 per cent in the future.

Survival periods for 104 patients with prostatic malignant disease who were managed conservatively are as follows:

	Living	Dead (or Untraced)
9 to 10 yr.	3	0
8 to 9 yr.	1	1
7 to 8 yr.	1	1
6 to 7 yr.	1	2
5 to 6 yr.	10	2
4 to 5 yr.	5	1
3 to 4 yr.	10	2
2 to 3 yr.	25	5
1 to 2 yr.	12	6
Less than 1 yr.	13	3
Total	81	23

Among the 18 patients who died, 9 are known to have died of carcinoma of the prostate gland, while 9 apparently died of other causes. Of 39 patients with demonstrable metastasis, 11 are dead or untraced; 6 have been under treatment for less than two years.

Lack of response to the drug was encountered in 8 patients. It is generally agreed that failure to respond to diethylstilbestrol is explained by a variation in the histologic pattern.

Relapses in patients under therapy were observed. However, they were not as frequent and rarely as severe as most investigators have reported. Our observations indicate that cessation of administration of the drug resulted in relapses in some patients. Among these further improvement was obtained by the use of additional diethylstilbestrol in a good proportion. The dose was increased above that of previous administration. In only a few cases the growth appeared to become independent to hormonal action during treatment.

SUMMARY

Records of 104 consecutive private patients having carcinoma of the prostate gland are reviewed. These patients were seen at frequent intervals.

Treatment in all instances was given in the form of diethylstilbestrol. Fifty-six (53.8 per cent) patients underwent transurethral resection for obstruction of the vesical neck. Surgical procedures for the relief of obstruction may be obviated by the initial administration of diethylstilbestrol in a fair proportion of patients. Lack of response to oral antiandrogenic therapy was unusual. Relapses while the patients were under therapy were not encountered as commonly as popular opinion indicated. Some relapses were traced to cessation of hormonal therapy.

Evidence is offered that prolonged control of prostatic cancer is accomplished by the use of antiandrogenic substance administered orally.

DISCUSSION

DR. S. W. MULHOLLAND, Philadelphia: The work of the essayists exemplifies the same paradoxic observations that we have made regarding hormones in reference to tumors of other organs, namely, that at one time a hormone will cause stimulation of growth and at other times a definite regression.

Endocrine therapy is affording relief from pain to many unfortunate old men, and months to years of comfortable life which they would not enjoy without it. Carcinoma of the prostate is increasing in frequency because of the increasing longevity with the aging of our population. The ultimate prognosis is poor because of late recognition of the disease and its slow growth or growth in the periphery of the gland where it fails to give typical urinary symptoms. Does this mean that our treatment of carcinoma of the prostate will continue to be largely a palliative measure? Our essayists have shown that this in itself is worth while. Reports show that only 30 per cent of patients treated (with hormones)

are dead at the end of a two year period. I like Dr. Hammer's choice of the words "antiandrogenic therapy," because it suggests that there may be still other substances, perhaps chemicals, which we may use in this attack on cancer of the prostate.

Radical prostatectomy gives 50 to 60 per cent of five year cures to compare with the figures cited. The urologist has been too conservative in attacking localized nodules in the prostate. Perineal exposure of the prostate can be easily carried out and the situation handled just as a nodule in the breast. If we do not do this, all our patients will fall into the group to be treated by endocrine therapy alone. Of late, larger doses of estrogen have been employed, with or without castration, and the number of patients receiving relief of pain for a short time has increased. We have used pain as an indication to increase dosage. Many patients reach levels at which the hormone (5 to 10 mg. daily) fails to relieve their pain or there is increased activity in the growth of the tumor. In these situations the dosage is increased until the pain disappears.

The size of the breasts is no indication of the amount of estrogen which it is safe to use. Castrates often have enlarged painful breasts after small doses, while less effect is noted on larger doses. Perhaps this is in keeping with Gardner's observation in mice, in which small doses of estrogen were a stimulant to the epithelium of the breast while larger doses caused atrophy.

DR. WILLIAM HERBST, Washington, D. C.: One aspect of this problem today seems to me to be the investigation of the chemical factors, and the other is the clinical management.

This contribution of Scott and his associates is remarkable in that it begins to give us a small pattern to fill out in our problem. The problem becomes pretty extensive. We have to take into consideration the pituitary, the thyroid, the pancreas and the gonads, all as part of the picture. The steroid patterns in these patients probably demand most of our immediate attention in view of the fact that variations in steroid chemistry seem to do more to influence the cell life in different types of tissues than any other one factor we know.

Some of the complications that we have experienced in the administration of estrogens are those of breast enlargement and pain. I do not think we should pay too much attention to these, and, if necessary, let us remove the breasts and continue our therapy.

We run into persons who have petechial disturbances in the skin. Calcium, as a general rule, will take care of that. Another complication is thrombophlebitis, which is a very unfortunate and rather serious complication. When this develops, we have to discontinue treatment with estrogens. There is also the problem of hot flashes. That is a rather mean one because there are instances in which nothing will control them. However, in most instances, the hot flashes may be somewhat controlled by the use of dexedrine® (d-amphetamine sulfate). That is not at all satisfactory in all the cases, but it is of some value.

We ought to have some plan rationalized from all the data that we have at the present time. A reasonable plan would be no chemical treatment in advanced carcinoma unless the patient is going downhill or pain is severe. When and if those symptoms occur, let us first castrate; then let us not give estrogens. When we do begin estrogens, let us start with the smallest possible dose, 1 mg. of stilbestrol and then build it up. I do not subscribe to the bombardment therapy of giving 15 mg. at one time. In regard to the control of pain, I think we may even resort to prefrontal lobotomy. In some cases it has merit.

In regard to life expectancy, the first series that I reported lived thirty-seven and a half months. Nesbit has done the most reliable comparative study in com-

paring a series of patients treated by castration and a series treated with estrogen. His conclusions were that the estrogen was just as efficacious.

We are dealing with a most complex problem, and it has been definitely contributory in our management of this problem. The problem involves general cell metabolism which goes into the field of specificity of action of various chemicals to various tissues. We can even produce hyperplasia in the kidney by the utilization of endocrine substance.

DR. HOWARD J. HAMMER, San Francisco: I should like to suggest, in reply to Dr. Herbst's observation on edema in patients under stilbestrol treatment, that not infrequently the edema of the lower extremities is of a transient nature and will disappear after prolonged therapy. Often swelling is due to thrombophlebitis rather than to ordinary edema or secondary to tumor extension, in which instance, perhaps, the giving of larger doses may be indicated. It is certainly something to think about.

Failures under hormonal therapy may well be due to cessation of the therapy on the part of the patient. I am sure that is true. We think we have observed that to our conclusive satisfaction.

DR. GERSHOM J. THOMPSON, Rochester, Minn.: The observation of Dr. Brendler, Dr. Chase and Dr. Scott that improvement will occur in patients suffering with cancer of the prostate with metastasis after injections of testosterone proprionate is certainly inconsistent with the theory that castration is beneficial for this disease. Whether or not in an uncastrated patient additional injections of testosterone plus repeated determinations of serum acid phosphatase might be helpful in making a diagnosis of occult metastasis remains to be seen. Such a test might be of value in a case under consideration for radical operation. Four of the 6 patients studied by the authors were benefited by testosterone therapy as evidenced by a gain in weight and other findings. They believed that in 1 patient the prostate gland decreased in size. This is distinctly contrary to what has been previously said to occur. Brendler and his associates significantly point out that although existing methods of endocrine manipulation have undoubtedly been of real benefit to many patients they have not provided the final answer in the treatment of malignant disease of the prostate.

Dr. Reynolds, Dr. Schulte and Dr. Hammer report consistently good results from antiandrogenic therapy and apparently feel that prolonged administration of estrogens is desirable. The survival rate which they report would seem to substantiate the opinion. They also say that relief of urinary obstruction by surgical methods may be obviated in a fair proportion of patients by early administration of diethylstilbestrol. I have seen an occasional case in which such therapy has permitted postponing surgical intervention for a number of months, but as a general rule when these patients have enough cause to seek medical advice they need surgical treatment.

I agree with Reynolds, Schulte and Hammer that extensive transurethral resection or other extensive surgical procedures can be avoided with profit to the average patient with prostatic carcinoma.

Doctor Baurys wisely brings out the fact that many patients with prostatic cancer should be kept under observation and should receive no active treatment whatever. His results in 143 patients who were treated surgically are most commendable. He directs attention to the fact that this malignant process is found in a much higher percentage of men in the eighth and ninth decades of life than in those younger. Extensive radical surgical procedures for these patients is undesirable.

One of the most striking things brought out in a recent study of the histories of 1,751 patients with prostatic carcinoma treated at the Mayo Clinic prior to 1945 was the fact that more than twice as many patients survived three years or more after treatment in the preceding decade when compared with those treated in the decade 1925 to 1935. This referred to patients treated only by transurethral resection and did not include any subjected to orchiectomy. This would seem to indicate that prostatic carcinoma is becoming less lethal as the years go on or that patients are being seen earlier and treated more promptly. Our statistics department tells me that the same strange increase in survival rate is noted in all types of malignant disease and is not confined to patients with prostatic carcinoma.

DR. ERNEST F. HOCK, Binghamton, N. Y.: A diagnostic procedure important in prostatic cancer is serum acid phosphatase. We had 1 patient who showed increased phosphatase and, on clinical examination, did not appear to have cancer of the prostate. Subsequent phosphatase tests gave normal results. We found that the patient had had a prostatic massage for a Papanicolaou stain a short time before the blood was taken for the serum acid phosphatase. We concluded that possibly the massage may have produced entry of prostatic secretion into the blood stream.

We subjected 20 patients to prostatic massage—outpatients taken at random. Acid serum phosphatase was taken before and at certain intervals after the prostatic massage. The serum acid phosphatase was increased in the majority of these cases after massage and reached carcinoma levels in 20 per cent of them. In a few cases the increase was significant up to five hours after the massage, but the levels were normal in all cases twenty-four hours later.

We decided from then on to do repeated phosphatase determinations in all cases in which high serum acid phosphatase levels did not agree with the clinical findings.

We had another case which was referred to me as one of prostatic carcinoma because the patient had a serum acid phosphatase level of 4.6 Bodanski units. A repeat phosphatase determination made two days later showed 0.2 Bodanski units. I believe that in this case the increase may have been due to straining during a bowel movement, which he had shortly before the blood was taken.

DR. HERBERT BRENDLER, Baltimore, Md.: I should like to say, with reference to Dr. Mulholland's remarks, that when we first thought of investigating the role of androgens in prostatic cancer we were struck by the results in the endocrine treatment of metastatic cancer of the breast, which is such a similar disease. We were especially interested in the results which had been reported, stating that androgens exerted a more beneficial effect in the younger age groups and estrogens in the older group.

We also wondered about the observation that androgens appeared to affect the osseous metastasis predominantly, whereas estrogens affected the cancer of the breast itself, as well as soft tissue metastasis. That led us to wonder whether an analogous situation existed with reference to prostatic cancer.

We were at that time investigating certain folic acid derivatives, which we thought might behave in an antiandrogenic manner. We felt that it was important to find out, before going ahead with a search for an antiandrogen, exactly what was the role of androgens in cases of prostatic cancer.

ANATOMIC STUDY OF THE PORTAL VEIN AND ITS MAIN BRANCHES

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With the Technical Assistance of Harriett L. Hills, A.B.‡
SAN FRANCISCO

THE ESTABLISHMENT of experimental portacaval shunts by Nikolai V. Eck [1] in 1877 laid the foundation for the consideration of the surgical correction of portal hypertension. According to Rosenstein,[2] this was followed by the surgical thought and experimentation of Talma, Bier, Jersulem and Frank. Rosenstein [2] and de Martel and Vidal [3] completed portacaval anastomosis by the side to side technic early in the twentieth century. The work of Gad,[4] Herrick,[5] McIndoe,[6] Burton-Opitz,[7] Thomson,[8] Barger and Dale,[9] Whipple and his asso-

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1. Eck, N. V.: On the Question of the Ligation of the Portal Vein, Voyenno-med. J. **130** (sect. 2) :1-2, 1877.

2. Rosenstein, P.: Ueber die Behandlung der Lebercirrhose durch Anlegung einer Eck'schen Fistel, Arch. f. klin. Chir. **98**:1082-1092, 1912.

3. De Martel, M. F., and Vidal, M. E.: Observations de fistule d'Eck chez l'homme, Rev. de chir. Paris **42**:1181, 1910.

4. Gad, J.: Studien über Beziehungen des Blutstroms in der Pfortader zum Blutstrom in der Leberarterie, Berlin, G. Schade, 1873.

5. Herrick, F. C.: An Experimental Study into the Increased Portal Pressure in Portal Cirrhosis, J. Exper. Med. **9**:93-104, 1907.

6. McIndoe, A. H.: Vascular Lesions of Portal Cirrhosis, Arch. Path. & Lab. Med. **5**:23-42 (Jan.) 1928.

7. Burton-Opitz, R.: The Vascularity of the Liver: I. The Flow of Blood in the Hepatic Artery, Quart. J. Exper. Physiol. **3**:297-313, 1910; II. The Influence of the Portal Blood-Flow upon the Flow in the Hepatic Artery, ibid. **4**:93-102, 1911; III. The Effect of Stimulation of Single Nerves of the Hepatic Plexus upon the Flow in the Hepatic Artery, ibid. **4**:103-125, 1911; IV. The Magnitude of the Portal Inflow, ibid. **4**:113, 1911; V. The Influence of the Greater Splanchnic Nerves upon the Arterial Inflow, ibid. **5**:83-90, 1912; VI. The Influence of the Greater Splanchnic Nerves upon the Venous Inflow, ibid. **5**:189-196, 1912.

8. Thomson, W. H.: Vasomotor Reactions of Liver, J. Physiol. **25**:1, 1899.

9. Barger, G., and Dale, H. H.: Ergotoxin and Some Other Constituents of Ergot, Biochem. J. **2**:249-299, 1907.

ciates,[10] Bayliss and Starling [11] and others laid the groundwork for the understanding of hepatic metabolism and blood flow in cirrhosis and in the presence of an Eck fistula. McIndoe [6] demonstrated that the arterial bed of the liver seemed to be spared more than the portal in cirrhosis. With the improvement in vascular surgery and advance in physiology and diagnosis, there has been renewed interest in the surgical relief of portal hypertension.[12]

During this period of physiologic and surgical advance, little attention was given to the study of the portal vein and its main branches from an anatomic standpoint. Blakemore and Lord [12b] in their consideration of portacaval anastomosis stated that four of six anatomists described the coronary vein as normally arising from the splenic vein and illustrated the main branches as shown by these anatomists (fig. 1). No two configurations are the same. Examination of seven more anatomic texts [13] showed decided lack of conformity in regard to the main branches of the portal system. Survey of the literature indicated that little had been done in this respect. Thomson [14] in 1889 and Mariau [15] in 1893

10. Whipple, G. H.; Robscheit-Robbins, F. S., and Hawkins, W. B.: Eck Fistula Liver Subnormal in Producing Hemoglobin and Plasma Proteins on Diets Rich in Liver and Iron, J. Exper. Med. **81**:171-191, 1945.

11. Bayliss, W. M., and Starling, E. H.: On the Origin from the Spinal Cord of the Vaso-Constrictor Nerves of the Portal Vein, J. Physiol. **17**:120-128, 1894.

12. (*a*) McIndoe.[6] (*b*) Blakemore, A. H., and Lord, J. W., Jr.: Technic of Using Vitallium Tubes in Establishing Portacaval Shunts for Portal Hypertension, Ann. Surg. **122**:476-489, 1945. (*c*) Whipple, A. O.: Problem of Portal Hypertension in Relation to the Hepatosplenopathies, ibid. **122**:449-475, 1945. (*d*) Gardner, R. H.; Leeds, F. H., and Freeman, N. E.: Experimental Portacaval Anastomosis, California Med. **69**:1-5, 1948. (*e*) Blalock, A.: The Use of Shunt or By-Pass Operations in Treatment of Certain Circulatory Disorders, ibid. **125**:129-141, 1947. (*f*) Whipple, A. O.: Recent Studies in the Circulation of the Portal Bed and of the Spleen in Relation to Splenomegaly, Tr. & Stud., Coll. Physicians, Philadelphia **8**:203, 1941. (*g*) Welch, C. S.: A Technique for Portacaval Anastomosis (Eck Fistula), Surg., Gynec. & Obst. **85**:492-494, 1947.

13. (*a*) Cunningham, D. J.: Cunningham's Manual of Practical Anatomy, New York, William Wood & Company, 1918. (*b*) Callender, C. L.: Surgical Anatomy, Philadelphia, W. B. Saunders Company, 1933. (*c*) Testut, L.: Traité d'anatomie humaine, Paris, O. Doin, 1921-1923, vol. 2, p. 351. (*d*) Allen, H.: A System of Human Anatomy, Including Its Medical and Surgical Relations, Philadelphia, H. C. Lea's Son & Co., 1884, sect. 4. (*e*) Grant, J. C. B.: A Method of Anatomy, ed. 3, Baltimore, Williams & Wilkins Company, 1944. (*f*) Quain, J.: Elements of Anatomy, edited by E. A. Schaefer, J. Symington and T. H. Bryce, London, Longmans, Green & Co., 1909. (*g*) Toldt, K., and Rosa, A. D.: Atlas of Human Anatomy for Students and Physicians, New York, The Macmillan Company, 1926.

14. Thomson, A.: Report of the Committee of Collective Investigation of the Anatomical Society of Great Britain and Ireland for the Year 1889-1890, J. Anat. & Physiol. **5**:99-101, 1889.

15. Mariau, A.: Recherches anatomiques sur la veine porte, et particulièrement sur ses anastomoses avec le système veineux général, Paris, O. Doin, 1893.

reported on the order of union of the three great trunks which form the portal vein and gave other miscellaneous information. Testut [16] described the formation of the portal vein and its length and diameter but did not state the number of cases on which this information was based. No morphologic or mensurative study of the portal vein and its major branches seems to have been done since the turn of the century.

This report embodies a summary of the embryologic and anatomic literature and a study of the portal vein and its main branches.

EMBRYOLOGIC ASPECTS [17]

Primitive blood vessels develop from angioblasts in the splanchnic mesoderm of the yolk sac as knots or masses called blood islands of Pander. There is first the formation of intercellular spaces containing

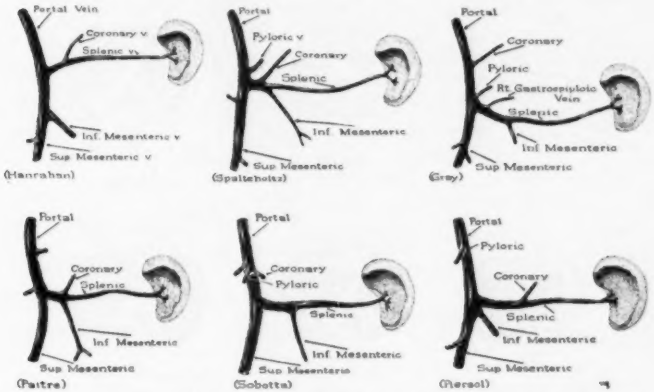

Fig. 1.—Configuration of portal vein and main branches as illustrated by six anatomists. (Redrawn from Blakemore and Lord.[12b])

16. (*a*) Testut.[13e] (*b*) Testut, L.: Porte (Veine), in Dechambre, A.: Dictionnaire encyclopédique des sciences médicales, Paris, V. Masson et Fils, 1888, vol. 26, pp. 713-720.

17. (*a*) Grant.[13e] (*b*) Gray, H.: Anatomy of the Human Body, ed. 23, Philadelphia, Lea & Febiger, 1936. (*c*) Arey, L. B.: Developmental Anatomy, Philadelphia, W. B. Saunders Company, 1930. (*d*) Jordan, H. E., and Kindred, J. E.: Textbook of Embryology, ed. 4, New York, D. Appleton-Century Company, 1942. (*e*) Fraser, J.; Kingsley, A., and Brown, M. B.: A Clinical Syndrome Associated with a Rare Anomaly of the Vena Portal System, Surg., Gynec. & Obst. **78**:520-524, 1944. (*f*) MacMahon, H. E.: Congenital Anomalies of the Liver, Am. J. Path. **5**:499-507, 1929. (*g*) Bardeen, C. R., and others: Manual of Human Embryology, edited by F. Keibel and F. P. Mall, Philadelphia, J. B. Lippincott Company, 1910-1912, vol. 20. (*h*) Keith, A.: Human Embryology and Morphology, London, Edward Arnold & Co., 1923. (*i*) Knight, H. O.: An Anomalous Portal Vein with Its Surgical Dangers, Ann. Surg. **74**:697, 1921.

primitive blood cells. These vacuoles anastomose to form capillary beds, with future capillaries being derived by sprouting or budding from the original bed. Similar development is seen in the embryonic mesoderm at a slightly later stage. Fusion of these two systems gives rise to paired dorsal aortas, anterior and posterior cardinal veins, subcardinal veins, umbilical veins and arteries and vitelline veins and arteries. These develop in areas of future main vascular channels, their fate being determined by genetic, metabolic and hydrostatic factors.

The basic ground plan for veins consists of: (1) paired umbilical veins in the lateral abdominal wall from the embryophore to the sinus venosus, (2) paired vitelline veins from the yolk sac to the umbilical veins at the sinus venosus and (3) paired anterior cardinal or precardinal

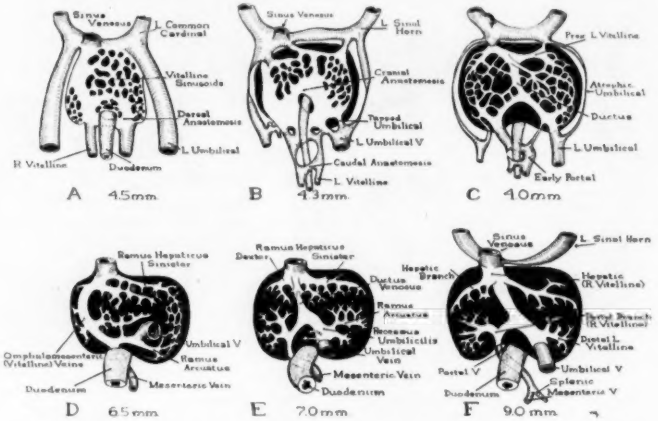

Fig. 2.—Invasion of the vitelline veins by the hepatic diverticulum and their transformation into the portal vein. (Adapted from Mall.[17g])

veins lateral to the nervous system, joining with paired posterior or postcardinal veins to form the common cardinal vein or duct of Cuvier.

The primitive septum transversum envelops the paired vitelline and umbilical veins as they approach each other to form with the ducts of Cuvier the caudal end of the heart (sinus venosus). A tubular ventral evagination from the gut invades the caudal portion of this transverse shelf of mesoderm and adjacent ventral mesentery. This tubular evagination is the hepatic diverticulum.

The vitelline veins are the first to be invaded by the hepatic tissue. The invaded region develops into the hepatic sinusoids (fig. 2*A*) and divides each vitelline vein into proximal and distal portions. The

proximal end of the left vitelline is reduced to sinusoids. Its blood flow shifts to the proximal end of the right vitelline vein, which enlarges to form the common hepatic vein and sinus venosus (fig. 2*C* to *F*). Slightly later three transverse anastomoses take place in the distal portions of the vitelline veins: (1) a cranial anastomosis in the liver ventral to the duodenum; (2) an intermediate anastomosis dorsal to the duodenum; (3) a caudal anastomosis ventral to the duodenum (figs. 2*B* and 3). This gives two venous rings which are soon interrupted: (1) the right vitelline vein degenerates between the caudal and inter-

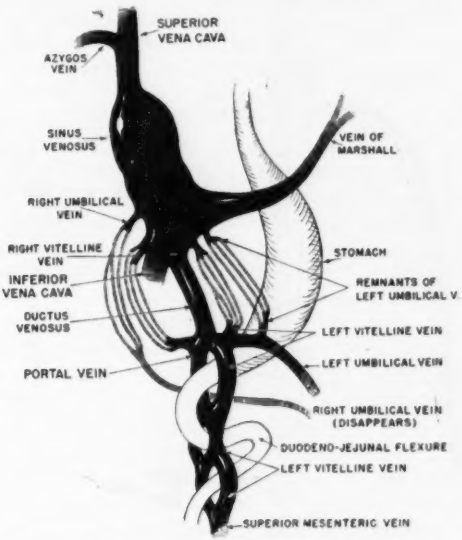

Fig. 3.—Development of the venous rings about the duodenum and their relation to the ductus venosus. (Redrawn from Keith.[17b])

mediate anastomoses; (2) the left vitelline vein between the intermediate and cranial anastomoses degenerates (fig. 2*C*). Thus, there is formed a special vitelline channel around the duodenum. The dorsal surface of the intermediate anastomosis receives a new vein from the mesentery of the bowel, i. e., the superior mesenteric vein, which becomes its chief venous drainage. The right vitelline vein degenerates back to the yolk sac, leaving the left vitelline vein, which, with the degeneration of the yolk sac, degenerates as far as its junction with the mesenteric vein. As a result the portal vein is constituted by (1) an intermediate anastomosis between the vitelline veins and (2) that portion of the right vitelline

vein which forms the right limb of the primitive cranial ring (figs. 2 *C* and *D* and 3). The hepatic veins are formed by the proximal portions of the vitelline veins.

Meanwhile, the ductus venosus has been forming; it is a direct continuation of the left umbilical vein, which has been enlarging as the right has been degenerating (fig. 3). Actually both proximal umbilical veins have degenerated, and the greater portion of the ductus venosus is a new channel. The blood from the placenta may now enter directly into the

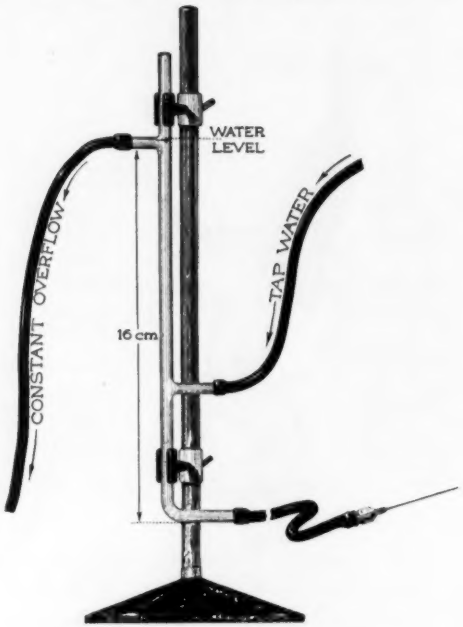

Fig. 4.—Diagram of overflow manometer.

vena cava and heart via this channel without entering the sinusoidal circulation. After birth the umbilical vein normally degenerates, as does the ductus venosus, leaving the ligamentum teres and the ligamentum venosum.

MATERIALS AND METHODS

Twenty-five dissections of the portal vein were done, using the unfixed upper abdominal sample removed at routine postmortem examination. The sample consisted of the intact block containing the liver, spleen, pancreas, stomach, duodenum, upper abdominal aorta and inferior vena cava. Twenty-one samples were from

adult bodies, ranging in age from 41 to 78 years, and 4 from bodies of full term stillborn infants, all demonstrating no gross or microscopic evidence of portal obstruction.

In these dissections an endeavor was made to identify the major branches of the portal and splenic veins. Special emphasis was placed on the identification of the coronary or left gastric vein because of its role in the production of esophageal varices. When possible, the length and width of the veins were measured. In measuring the width, the transverse measurement of the collapsed vein was considered as its diameter. To establish this measurement as valid, an overflow manometer (fig. 4) was connected to a previously dissected portal vein in which the main vessels had been distally ligated. The vein and its main tributaries were then dilated under 16 to 17 cm. of water pressure and the diameter measured and compared to the diameter of the vein collapsed. In the three specimens so studied the measurements compared within 0.1 cm.

Further information was obtained from examination of 36 fixed cadavers in the anatomic laboratory.

PORTAL SYSTEM

The portal system includes all veins which carry blood from the abdominal part of the digestive tube, the spleen, pancreas and gallbladder to the liver, entering at the porta hepatis in two main branches, one to each lobe of the liver. However, it may rarely enter directly into the vena cava without traversing the liver,[18] or, as in the case of an anencephalic monster described by Mead,[19] it may directly enter the right auricle. Rothe and Hyrtl [19] have also reported similar observations. Huber and Morgani [19] wrote of a supradiaphragmatic anastomosis of the subhepatic veins with the inferior vena cava. Knight [17i] reported a splenic vein which crossed posterior to the midpancreas, emerging just below the pancreatic neck; it then passed along the summit of the duodenojejunal flexure and anterior to the head of the pancreas, being joined by two mesenteric veins to run anterior to the superior duodenal loop and into the lesser omentum anterolateral to the common bile duct and hepatic artery. This appears to be a case of degeneration of the posterior cephalad loop and the anterior caudal loop, with persistence of the corresponding anterior and posterior portions of the vascular loops. Schnitzler [20] reported a similar case, with compression of the duodenum by the anterior cephalad loop and resultant stenosis. Fraser, Kingsley and Brown [17e] encountered surgically a case in which both caudal and cephalic loops persisted, giving a small portal vein in normal position with an anterior portal channel demonstrating itself as multiple vari-

18. Testut.[13c] Allen.[13d] Testut.[16b] M'Donnell, R.: Observations on Anatomy and Physiology of the Kidney, Glasgow M. J. **2**:285-295, 1854-1855. Abernethy, J.: Transposition of Viscera Coexisting with Entry of Portal Vein into Vena Cava, Phil. Tr. **17**:296, 1809.

19. Cited by Testut.[13c]

20. Schnitzler, J.: Ueber eine eigentümliche Missbildung mit Stenosierung des Magenausgangs, Med. Klin. **22**:723-725, 1926.

cosities. Many anomalies and degenerative changes have been recorded, such as congenital absence, cavernomatous transformation or degeneration, congenital atresia and absence of the inferior vena cava, with its tributaries emptying into the portal vein.[21] All these major anomalies of the portal vein are, however, quite rare, with the exception of cavernomatous transformation, which in most cases seems to be a postnatal event rather than a congenital anomaly.

The peculiarity of the portal system is that it ramifies into two capillary beds between the abdominal viscera and the vena cava. It is a venous system without valves in the larger channels. Sappey,[22] Hochstetter [23] and Wilkie [24] all reported valves in the smaller tributaries of the stomach. These were sharply restricted to the area of the stomach, i. e., occurring in those vessels draining into the coronary, epiploic or short gastric veins, few or none being seen in the esophagus or beyond the pyloric ring. There is usually one valve which lies at the junction of the smaller tributaries with the larger channels. This is a bicuspid valve, consisting of a basement membrane and one layer of flattened epithelium. Such valves can also be found in the mesenteric veins, especially those to the colon. They are easily seen in the newborn

21. Testut.[16b] Thomson.[14] Bernard, C.: Note sur une novelle espèce d'anastomoses vasculaires, Arch. gén. de méd. **23**:360-362, 1850. Natali, C.: Mancato sviluppo del tronco principale della vena porta, Monitoire zool. ital. **39**:150-158, 1928. Beitzke, H.: Ueber einen Fall von kavernöser Umwandlung der Pfortader, Charité-Ann. **34**:466, 1910. Hart, C.: Ueber die cavernöse Umwandlung der Pfortader, Berl. klin. Wchnschr. **1**:2231-2234, 1913. Meyer, F. G.: Ueber kavernöse Umwandlung der Pfortader, Med. Klin. **16**:880-883, 1920. Hulk, J. F.: Cavernous Changes Around the Portal Vein, Nederl. tijdschr. v. geneesk. **67**:4-16, 1923. Aschner, B.: Zur Klinik des Pfortaderkavernoms, Wien. med. Wchnschr. **78**:762-764, 1928. Drechsel, J.: Anomalie des Recessus umbilicalis mit Linkslage der Gallenblase, Ztschr. f. d. ges. Anat. (Abt. 1) **91**:638-643, 1940. Pernkopf, E.: Eine seltene Anomalie im Verlaufe des Pfortaderstammes, zugleich ein Beitrag zur Entwicklungsgeschichte der Pfortader beim Menschen, ibid. **97**:293-330, 1932. Klemperer, P.: Cavernomatous Transformation; Relation to Banti's Disease, Arch. Path. **6**:353-377 (Sept.) 1928. Cabred, R. G.: Considerationes sobre un raro tumor angiocavernomatoso del tronco porta, Semana méd. **1**:109-127, 1926. van Creveld, S., and Levy, W. A.: Cavernous Malformation About the Portal Vein Manifested Clinically as a Chronic Thrombosis of the Splenic Vein, Am. J. Dis. Child. **39**:790-806 (April) 1930. Schrank, A.: Ein seltener Fall von abnormer Pfortaderverengung und -Aufspaltung, Klin. Wchnschr. **19**:1217-1218, 1940. Martos, J.: Pfortadersklerose und kavernöse Umwandlung infolge Appendicitis, Arch. f. klin. Chir. **185**:322-330, 1936.

22. Sappey, C.: Recherches sur quelques veines portes accessoires, Mem. Soc. de biol. **11**:3-13, 1859.

23. Hochstetter, F.: Ueber das normale Vorkommen von Klappen in den Magenverzweigungen der Pfortader beim Menschen und einigen Säugethieren, Arch. f. Anat. u. Entwcklngsgesch. 137-142, 1887.

24. Wilkie, D. P. D.: On the Presence of Valves in the Veins of the Portal System, Brit. M. J. **2**:602-604, 1911.

infant; however, with increase in age these valves become insufficient so that their cusps no longer oppose. The valves of veins in man and monkey are similar, and it is only in the Carnivora that they seem to assume importance in relation to visceral circulation. These valves are similar to those seen in the systemic veins.[25]

In this entire series of dissections, no valves were encountered in the main branches of the portal system. Valves as previously described were encountered in the dissection of stillborn infants.

In the entire series of dissections, no major anomalies of the portal vein were encountered other than in one case (a cadaver) in which intestinal branches from the jejunum reached the main portal stem via a peritoneal fold over the third portion of the duodenum. There was concomitant observation of a horseshoe kidney.

PORTAL VEIN

Consideration of the portal vein from a surgical standpoint with special regard for the technical aspects of portacaval anastomosis makes important its morphology and mensuration.

The portal vein in 85 per cent of the total 54 dissections (Thomson [14] reported 93 per cent of 118 cases) was formed by the union of the superior mesenteric vein and the splenic vein just posterior to the head of the pancreas at about the level of the second lumbar vertebra and extended slightly on the right of midline to the porta hepatis, where it divided into two branches before entering the liver. In about 15 per cent of cases it was formed by the union of the superior mesenteric, the inferior mesenteric and the splenic veins. The divisions into right and left branches at the porta hepatis were extrahepatic in about 85 per cent of cases. On measurement of the superior angles in each case, the vein made an angle at the midline with the midsagittal plane of approximately 55 to 75 degrees and with the inferior vena cava of between 100 and 120 degrees. The proximal portion and the right branch overlaid the inferior vena cava. The expansion of the transversalis fascia, as the prerenal fascia of Gerota, overlaid the vena cava and abutted against the dense areolar membrane of the posterior wall of the lesser omental fold, making easy the exposure of these two vessels if the correct cleavage plane was obtained. These relations were established by dissection and by venography with 10 per cent sodium iodide solution injected into the superior mesenteric vein of the intact fresh cadaver (figs. 5 and 6).

The smaller tributaries of the portal vein consisted mainly of the coronary, pyloric, cystic and irregular pancreaticoduodenal branches.

25. Brinton, J. H.: Description of a Valve, at the Termination of the Right Spermatic Vein in the Vena Cava, with Remarks on Its Relations to Varicocele, Am. J. M. Sc. **32**:111-118, 1856.

Of these, the coronary vein is of interest because of its role in production of esophageal varices. The coronary or left gastric vein and its accompanying pyloric vein took their origin from the portal vein in 68 per cent of a total of 59 dissections (Thomson [14] reported 69 per cent of 26 dissections), from the junction of the splenic and superior mesenteric veins in 8 per cent and from the splenic vein in 24 per cent of cases (fig. 5). Histologically, the portal vein differs from the veins of the

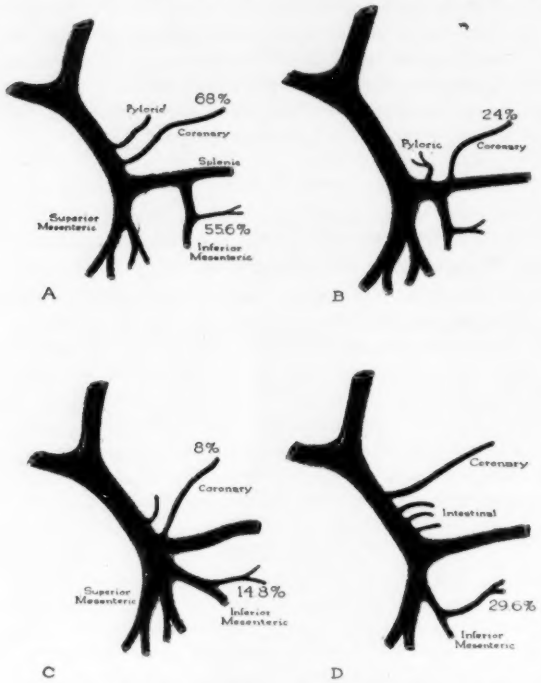

Fig. 5.—Variations in the morphology of the portal vein.

extremities and follows the pattern of visceral veins in losing much of its circular muscle fibers and being constituted in the greater part by longitudinal fibers interspersed with areolar tissue with small amounts of elastic tissue.[26]

26. Grant.[13e] Fraser and others.[17e] Bailey, F.: Text-Book of Histology, Baltimore, William Wood & Company, 1936. Maximow, A. A., and Bloom, W.: Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1930. Piersol, G. A.: Text-Book of Normal Histology, Philadelphia, J. B. Lippincott Company, 1893.

Fig. 6.—Postmortem roentgenogram of portal system injected with 10 per cent sodium iodide solution.

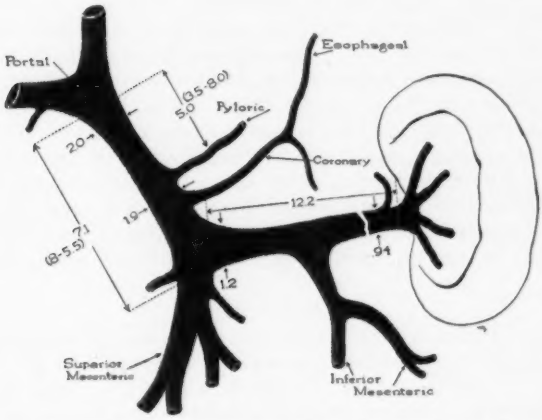

Fig. 7.—Mensuration of the portal vein and its main branches. Figures are in centimeters.

In 23 adult specimens the measurements of the length of the portal vein were made (fig. 7). The average length was found to be about 7 cm., with a maximum of 8 and a minimum of 5.5 cm. This was measured from the point at which the projected midline of the right and left branches forming the vein met to the projected midline of the right and left branches of the portal vein at the porta hepatis. This result compares fairly well with the measurements of Testut,[13c] who stated the length to be 8 to 10 cm. but defined the vein as extending from the formation at the head of the pancreas to the porta hepatis. Gray [17b] placed the length at 8 cm. and Allen [13d] at 7.5 cm., but they did not define the measurement.

An upper segment of the portal vein occurred above the highest branch to the junction of the right and left portal veins at the porta hepatis which had an average length in 16 cases of 5 cm., with a maximum of 8 and a minimum of 3.5 cm. This indicates that there is an upper segment where surgical dissection can be begun without fear of major hemorrhage.

In 17 cases the width of the portal vein was measured (fig. 7). The proximal measurement averaged 2 cm., with a span of 1.3 to 3.2 cm. Distally or just above the junction with a splenic vein, it averaged 1.9 cm. with 1.1 cm. minimum and 3 cm. maximum. These figures are somewhat larger than those quoted by Testut,[13c] but here we measured the width of the vein transversely and collapsed (one-half the circumference), as previously defined, rather than the diameter.

SUPERIOR MESENTERIC VEIN

This vein is formed by tributaries from the small intestine, colon and head of the pancreas, and irregularly from the stomach via the right gastroepiploic vein. Its position is predominantly ventral and to the right of the superior mesenteric artery. It receives inconstantly the inferior mesenteric vein (29 per cent of 54 dissections; fig. 5). It is a short vein forming from multiple tributaries as they cross the third portion of the duodenum just to the right of the duodenojejunal junction and approach the uncinate process. No attempt to measure the caliber of this vessel was made because of its multiple irregular tributaries, some of which entered the vessel at its junction with the splenic vein.

SPLENIC VEIN

The splenic vein derives its blood from the spleen, the greater curvature of the stomach and the pancreas, and irregularly from the left part of the colon and the rectum. The splenic veins (five to fifteen channels) originate at the splenic hilus and join near the tail of the pancreas, after free anastomosis with themselves and with the short gastric vessels to form the main splenic vein (fig. 5). The left gastroepiploic vein enters

the main splenic vein usually just after its formation. Rarely it enters one of the superior splenic tributaries in the splenic pedicle. The vein proceeds in a more or less transverse direction in the body and head of the pancreas, lying generally inferior and ventral to the artery, and usually is visible on the ventral surface of the tail of the pancreas. It receives many small tributaries from the substance of the pancreas and inconstantly pancreaticoduodenal branches near the head of the pancreas. In 24 per cent of 59 dissections the coronary and pyloric veins entered the proximal one third of the splenic vein and in 7 per cent of the dissections entered at the junction of the splenic and superior mesenteric veins (fig. 5 *B*). The inferior mesenteric veins draining the left part of the colon and the rectum entered the splenic vein in 55.6 per cent of a total of 54 dissections, 14 per cent entering at the junction of the superior mesenteric and splenic veins (fig. 5 *A*, *C* and *D*). In 17 fresh dissections the splenic vein had an average length of 12.2 cm., with a span of 11 to 16 cm. In 7 cases the average width of the splenic vein at its origin was 0.94 cm., with a span of 0.6 to 1.8 cm., and at its mesenteric junction the width was 1.2 cm., with a span of 0.6 to 1.8 cm., all measured transversely and collapsed (fig. 7).

SUMMARY

The portal vein develops from the vitelline veins at the level of the caudal portion of the hepatic diverticulum, as it invades the septum transversum. Major anomalies of the main portal trunks are infrequent. The portal vein is formed by the union of the splenic and superior mesenteric veins (85 per cent of 54 dissections) and is approximately 5.5 to 8 cm. in length.

The pyloric and coronary veins usually enter the lower one third of the portal vein (68 per cent of 59 dissections). There is usually an upper segment of the portal vein averaging 5 cm. in length which is devoid of major branches. The inferior mesenteric vein usually enters the medial one third of the splenic vein (55.6 per cent of 54 cases).

RECONSTRUCTION OF THE BILE DUCTS WITH AN ISOLATED SEGMENT OF JEJUNUM

An Experimental Study

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AND
WILLIAM T. FITTS Jr., M.D.
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STRICTURES of the bile ducts remain a serious surgical problem. Despite the numerous reconstructive procedures that have been tried,[1] many patients eventually succumb with recurrence of the stricture, repeated attacks of cholangiohepatitis and progressive damage to the liver.

End to end suture of the divided ends of the bile ducts, if performed without undue tension, has given the best results. Unfortunately this procedure is not always possible, particularly when long segments of the ducts have been destroyed or when the defect extends into the hilus of the liver. By mobilizing the duodenum and, when necessary, splitting the head of the pancreas for identification of the distal duct, Lahey [2] and Cattell [3] have extended the scope of primary anastomosis of the duct ends. When this method is not feasible, one must choose between preserving the sphincter of Oddi by bridging the defect and by-passing the sphincter of Oddi by anastomosing the proximal duct directly to some portion of the intestinal tract.

The necessity of preserving the sphincter mechanism is not yet settled. Some [4] believe that its preservation is essential in the prevention of repeated attacks of cholangiohepatitis and progressive hepatic damage. Experimental studies carried out in our laboratory support

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From the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania.

1. Horgan, E.: Reconstruction of the Biliary Tract: A Review of All the Methods That Have Been Employed, New York, The Macmillan Company, 1932.

2. Lahey, F. H.: Further Experiences with Injured Bile Ducts, New England J. Med. **240**:161, 1949.

3. Cattell, R. B.: Benign Strictures of the Biliary Ducts, J. A. M. A. **134**:235 (May 17) 1947.

4. (*a*) Cole, W. H.; Reynolds, J. T., and Ireneus, C., Jr.: Strictures of the Common Duct, Ann. Surg. **128**:332, 1948. (*b*) Lahey.[2]

this hypothesis.[5] The operations of Allen[6] and Cole,[4a] in which the proximal duct is anastomosed to a defunctionalized jejunal loop, were devised to provide an "artificial sphincter" when the sphincter of Oddi itself cannot be utilized. On the other hand, it cannot be denied that many patients have had a satisfactory clinical result after direct anastomosis of the proximal duct to the duodenum as long as a free flow of bile is maintained, as emphasized by Walters.[7]

Operations which preserve the sphincter mechanism by bridging bile duct defects have usually failed, probably because the tissues used have not had an independent blood supply (e. g., vein, ureter) or have not had a mucosal lining (e. g., omentum). In the experiments described here, defects of the bile ducts in dogs were bridged with an isolated segment of jejunum— tissue with both an independent blood supply and a mucosal lining. To our knowledge this method has not been previously used.

EXPERIMENTAL METHODS

Mongrel dogs averaging 12 Kg. in weight were used. The abdomen was opened through an upper midline incision, with the animals under anesthesia induced by intravenous injection of pentobarbital sodium. At a point about 12 cm. distal to the duodenum an isolated jejunal loop was prepared. A jejunal segment about 2.5 cm. long and its subjacent jejunal vessels were isolated by dividing the jejunum and its mesentery proximally and distally (fig. 1). Intestinal continuity was restored by end to end anastomosis of the proximal and distal jejunum. The jejunal loop was brought through an opening in the transverse mesocolon to the subhepatic fossa, where it was incorporated, by two methods, in the extrahepatic biliary system. In the first method (fig. 2 *A*) the proximal end of the jejunal loop was anastomosed to the fundus of the gallbladder and the distal end was closed. The common bile duct was divided, and the proximal end was ligated. The distal end of the bile duct was anastomosed to a small opening made near the closed end of the jejunal loop. The short arms of a rubber T tube were passed through both anastomoses, and the long arm was brought out through a slit on the antimesenteric surface of the jejunal loop, ligated and covered with omentum. This procedure was done in 4 animals.

In the second method (fig. 2 *B*) both ends of the jejunal loop were closed and a short segment of the common bile duct was excised. The proximal and distal ends of the bile duct were anastomosed, over a rubber T tube or a straight plastic (polyethylene) tube, to small openings made in the sides of the jejunal flap. This procedure was done in 5 animals. T tubes were used in 3 and plastic tubes in

5. Fitts, W. T., Jr.; Cooper, D. Y., and Lazatin, C.: The Role of the Sphincter of Oddi in the Prevention of Cholangitis: Data Presented in the Forum on Fundamental Surgical Problems, American College of Surgeons, Los Angeles, Oct. 22, 1948.

6. Allen, A. W.: Method of Re-Establishing Continuity Between Bile Ducts and Gastro-Intestinal Tract, Tr. South. S. A. **58**:28, 1945.

7. Walters, W.: Stricture of the Bile Ducts, in Christopher's Textbook of Surgery, Philadelphia, W. B. Saunders Company, 1949.

2. One of the T tubes was removed at a second operation. The plastic tubes passed spontaneously. When the animals were killed, the biliary tract and liver were examined for evidence of stricture formation, biliary stasis and cholangitis. Sections of liver and the suture lines were examined microscopically.

RESULTS

Nine animals survived the operation and early postoperative period. Two died within two weeks of distemper. At autopsy biliary drainage appeared to be satisfactory and the suture lines were intact.

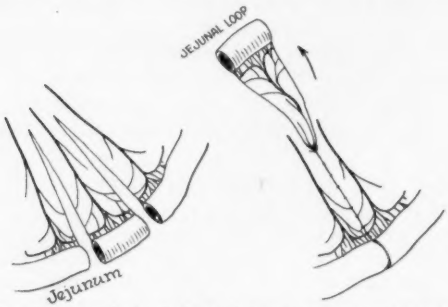

Fig. 1.—Preparation of the isolated jejunal segment, which is brought up through the transverse mesocolon to the biliary ductal system.

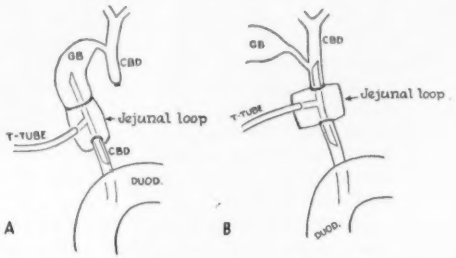

Fig. 2.—*A*, first method of incorporation of the jejunal loop in the biliary drainage system. *B*, second method.

The remaining 7 animals had an uneventful postoperative course. Four were killed between the third and the fifth month after operation, with their T tubes still in place. A photograph of one of these animals at autopsy is shown in figure 3. Although two of the T tubes contained plugs of biliary sediment, there appeared to be a free flow of bile around the tubes. There was no evidence of stricture formation or cholangiohepatitis, and the liver was normal on histologic examination in all instances.

One of the T tubes was removed at a second operation four months after the primary operation, and the animal was killed four months later. Figure 4 shows a probe passed through the proximal and distal bile duct and the intervening jejunal flap. A photomicrograph of the anasto-

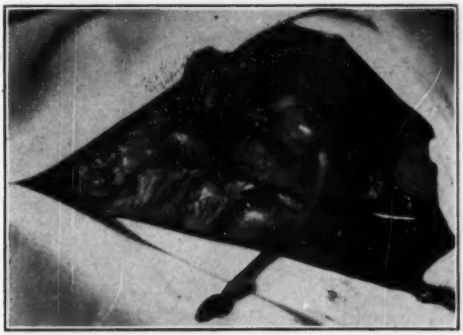

Fig. 3.—Photograph of an animal killed five months after operation. The jejunal loop bridges a defect of the common bile duct. The end of the T tube had been buried in omentum.

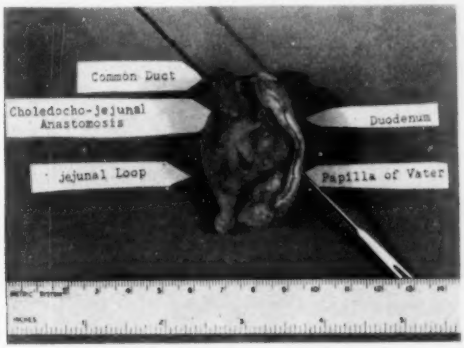

Fig. 4.—A specimen removed eight months after the primary operation (method 2) four months after removal of the T tube. A probe has been passed through the proximal and distal bile duct and the intervening jejunal loop.

motic suture line from this specimen is shown in figure 5. There was no tendency to stricture formation and no biliary stasis.

The 2 animals in which the second method of anastomosis (fig. 3) was done over plastic tubes were killed at nine and thirteen months after

Fig. 5.—Photomicrograph showing the junction of jejunal and choledochal mucosa. All the suture lines examined had a similar appearance.

operation. The tubes had passed at an unknown time in both instances. There was no evidence of stricture formation, and biliary drainage appeared to be normal. Photographs of the ductal system of 1 of these animals are shown in figure 6.

Since the lumen of the jejunal loop was larger than that of the bile ducts anastomosed to it, evidence of biliary stasis in the loop was sought for in all the animals. In none was there biliary sediment or stagnant bile.

COMMENT

In these experiments an isolated jejunal loop appeared satisfactory, both anatomically and functionally, for bridging bile duct defects. The blood supply of the jejunal segment was well maintained in its trans-

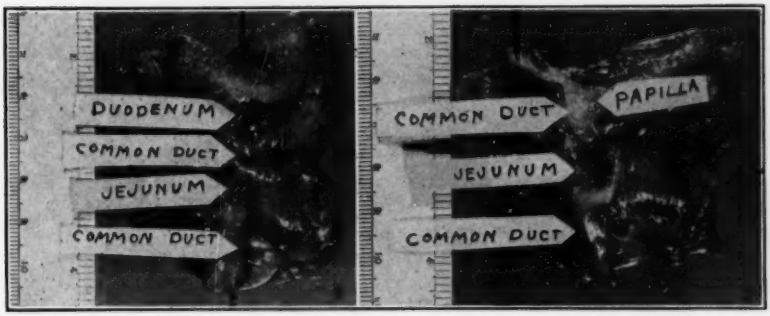

Fig. 6.—*A*, specimen removed thirteen months after anastomosis by the second method (fig. 2 *B*) over a polyethylene tube. *B*, same as *A*, with the proximal and distal bile duct and intervening jejunal loop opened. The proximal and distal suture lines show no evidence of constriction.

posed position. Mucosa to mucosa healing occurred, without evidence of stricture formation. Stasis did not occur within the jejunal loop even though its lumen was larger than that of the bile ducts. Resection of a portion of the antimesenteric border of the jejunal loop, reducing the size of the lumen to approximately that of the bile ducts, might be preferable.

Choledochojejunal anastomoses in patients have, in some instances, undergone stricture formation. Cholangitis due to reflux may have been largely responsible. With the protection of the sphincter mechanism, an anastomosis of the bile duct to the jejunum may have no greater tendency to stricture formation than an anastomosis of the divided ends of the bile duct. The choledochojejunal anastomoses in these experi-

ments, protected by the sphincter mechanism, did not apear to be undergoing stricture formation during the observation period of thirteen months.

SUMMARY

In order to provide tissue with an independent blood supply and a mucosal lining, isolated jejunal segments were used to bridge defects of the bile ducts in dogs. Stricture formation, biliary stasis and cholangiohepatitis did not occur in animals observed up to thirteen months after operation.

COMMINUTED FRACTURES OF THE OS CALCIS

Choice of Treatment

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A LARGE proportion of comminuted fractures of the heel terminate in prolonged pain and disability; such poor results are due partly to the trauma but even more so to improper treatment. Many practitioners, being misled by the absence of severe pain and external deformity, consider these fractures of minor importance and give them little attention. The disability which follows these injuries, however, is realized by the insurance companies. Recently the orthopedic consultant to one of the companies reviewed 100 cases and found that the average time lost from work after comminuted fractures was eighteen months, with an average payment of $1,561 for compensation during that time. There was a decided permanent disability in almost every instance.

In treating these fractures some surgeons are so skeptical about the results that they recommend practically nothing for them, while others have been so radical as to excise the heel or to amputate on account of permanent pain. Such a wide variation of opinion indicates a general misunderstanding of these injuries and the need of a simple classification for their proper treatment.

I have made a critical analysis of 50 consecutive comminuted fractures which I treated and followed. As a result of this study I feel that a sharp distinction should be made between the comminuted fractures which can be treated by conservative methods and those which should be treated radically to obtain the best results. It is practical to divide them into type A, fractures which do not involve articular surface, and type B, fractures involving articular surface.

TYPE A. FRACTURES NOT INVOLVING ARTICULAR SURFACE

The commonest example of this type of fracture occurs in the posterior third of the heel. A severe compression force produces flattening or "loss of the tuber angle," and in many cases there is also spreading and tilting of the bone, but the lines of fracture do not involve the subastragalar or calcaneocuboid joints. Failure to correct a diminished tuber angle does not terminate in a painful disability, but the consequent

From the Department of Orthopaedic Surgery and Fractures, Hahnemann Hospital.

laxity of the tendo achillis eliminates the spring in walking and prevents rising on tiptoe. Slight spreading or tilting of the heel is not disabling, although decided displacement causes permanent pain from faulty weight bearing and arthritis.

Treatment.—Fractures in which the heel is not decidedly displaced need no manipulation; the most satisfactory treatment is early, protected weight bearing in a walking cast, the foot being held in a decided equinus position. Thus, protected function preserves muscle tone and prevents degenerative changes in the joints, which otherwise would occur from nonuse. Such injuries respond well to this treatment, even in elderly patients.

More severe injuries, with loss of the tuber angle and decided squashing and tilting, must be treated by reshaping. The method of Hermann [1] is satisfactory for these, in which a Steinmann pin is inserted through the posterior tuberosity for correction of the angulation, and

Fig. 1.—Fracture of os calcis, without involvement of articular surface. The tuber angle is diminished by the displacement. Treatment indicated is reshaping, followed by protected weight bearing. (Modified from Watson-Jones.)

the lateral spreading is corrected with the clenched hands or with a clamp. In some instances it is of advantage to insert the Steinmann pin posteriorly for leverage instead of laterally for traction. A well padded cast then should be applied, including the pin if used, the plaster being molded over the lateral surfaces of the heel. Four weeks after injury, when the swelling has subsided, a new cast should be applied with only a little padding. Eight weeks after the injury a walking cast should be applied with the foot in a decided equinus position for bearing weight on the ball of the foot during the next four weeks. This plan of treatment has been found satisfactory, as it is simple, corrects the deformity and permits the earliest possible function with a minimum of muscular atrophy.

1. Hermann, O. J.: Conservative Therapy for Fractures of the Os Calcis, J. Bone & Joint Surg. **19**:709 (July) 1937.

The results of 23 consecutive comminuted fractures not extending into the joint surfaces which have been treated and observed by me since 1938 are shown in table 1.

A good result indicates ability of the patient to return to work without pain or disability, a fair result indicates ability to walk with little or no pain and return to at least light work and a poor result indicates severe pain and inability to return to regular work. These injuries were obviously less severe than those recorded in table 2. No manipulation was necessary for some, but manipulation and transfixion was

Fig. 2.—Conservative treatment, for fractures not involving articular surface. Early, protected weight bearing prevents severe muscular weakness; with the equinus position, weight is borne on the forefoot. The plaster must extend to the midthigh, the knee being slightly flexed.

TABLE 1.—*Fractures of Os Calcis Not Involving Articular Surface (No Operation)*

Total number of fractures		23
Average age of patients		50.0 yr.
Average time from injury to reemployment		5.4 mo.
Average permanent disability rating		4.7%
Final results	Good (20 cases)	87%
	Fair (3 cases)	13%
	Poor (0 cases)	0%

necessary for others. The usual period of disability following the use of plaster and crutches was greatly reduced by protected function in a walking cast.

This group of patients includes both men and women, some of whom performed housework or light mechanical work. It is readily understood that in a similar series composed entirely of industrial workers the disability rating would have been greater.

TYPE B. FRACTURES INVOLVING ARTICULAR SURFACE

All comminuted fractures extending into one or more joints are included in this classification, as there is a probability of permanent pain and disability in every instance when a weight bearing joint is so involved. Both heels often are affected similarly, as the typical injury is produced by falling in a standing position. In many cases there is flattening of the heel and loss of the tuber angle, with decided broadening and valgus deformity. The lines of fracture commonly extend into the subastragalar joint, but in addition there may be a fracture and displacement involving the calcaneocuboid joint.

Fig. 3.—Comminuted fracture, with involvement of the subastragalar joint and depression of fragments (modified from Watson-Jones, R.: Fractures and Joint Injuries, ed. 3, Baltimore, Williams & Wilkins Company, 1943). Operative treatment is indicated.

Treatment.—Permanent disability after such injuries is common on account of damage to the articular surface of the heel and the consequent aseptic necrosis or traumatic arthritis which develops. Reduction by manipulation obviously does not satisfy the requirements; in the most recent report on this method by Page and Mumford [2] 18 per cent of the results were fair or poor and an additional 5 per cent were extremely poor. These figures are about the same as those reported previously by Hermann. Böhler's [3] multiple pin traction and its modifications emphasize only the restoration of the tuber angle and correction of the lateral squashing, without attention to the joint involvement. Various

2. Page, W. A., and Mumford, E. B.: Fractures Involving the Articular Surfaces of the Os Calcis, S. Clin. North America **25**:161, 1945.

3. Böhler, L.: The Treatment of Fractures, ed. 4, Baltimore, William Wood & Company, 1935.

reports indicate that such treatment alone is not satisfactory, as many patients have permanent pain and disability. It is obvious, then, that these injuries need more than the usual treatment of joint fractures by reduction, immobilization and exercises. For reasonable certainty of the end result, I propose that a fusion operation be done routinely and early for every comminuted fracture with joint involvement and not as a last resort after many months of unsuccessful conservative treatment. This operation, although radical, is dependable in preventing pain and minimizing disability; furthermore, the subsequent period of immobilization is not longer than with the unpredictable conservative treatment.

Consideration of Technic.—For fractures with decided displacement, an arthrodesis through a lateral approach as recommended by Wilson [4] and by Conn [5] can be used satisfactorily, although this operation usually is performed after several weeks of immobilization. Gallie's [6] posterior arthrodesis of the subastragalar joint can be performed rather easily; however, this approach is not satisfactory for displaced fractures, unless preceded by the multiple pin traction described by Harris.[7] Palmer [8] has recently described an operation for early open reduction and replacement of the depressed cancellous fragments, but as no fusion of the broken articular surfaces is produced this method does not seem dependable. The method of open reduction and internal fixation described by Whittaker also does not take into consideration the joint injury and the consequent disability.

Choice of Operation.—In order to obtain the best results in such a difficult group of fractures a standardized plan of operative treatment is suggested.

A. For all comminuted fractures which involve the subastragalar joint, without decided loss of the tuber angle or lateral squashing deformity, a fusion operation should be performed routinely. This arthrodesis is accomplished most easily by Gallie's method.

B. For fractures with decided valgus deformity from collapse of the cancellous bone I recommend a subastragalar arthrodesis by a lateral approach, supplemented by packing with bone blocks. For this

4. Wilson, P. D.: Treatment of Fractures of the Os Calcis by Arthrodesis of the Subastragalar Joint: Report on 26 Cases, J. A. M. A. **89**:1676 (Nov. 12) 1927.

5. Conn, H. R.: Fractures of the Os Calcis, J. Bone & Joint Surg. **17**:2 (April) 1935; Fractures of the Os Calcis, in American Academy of Orthopaedic Surgeons Lectures on Reconstruction Surgery, Ann Arbor, Mich., Edwards Brothers, 1944, pp. 137-147.

6. Gallie, W. E.: Subastragalar Arthrodesis in Fractures of the Os Calcis, J. Bone & Joint Surg. **25**:731 (Oct.) 1943.

7. Harris, R. I.: Fractures of the Os Calcis: Their Treatment by Tri-Radiate Traction and Subastragalar Fusion, Ann. Surg. **124**:6 (Dec.) 1946.

8. Palmer, I.: The Mechanism and Treatment of Fractures of the Os Calcis, J. Bone & Joint Surg. **30-A**:1 (Jan.) 1948.

operation, which both corrects the deformity and fuses the joint, it is not necessary to use preliminary traction as described by Harris. If the tuberosity angle must be corrected, a Steinmann pin can be inserted lengthwise through the posterior portion of the heel and left in place.

Fig. 4.—Posterior block arthrodesis (Gallie's technic). This is a dependable method when there is no gross displacement. It is unsatisfactory for fresh fractures with a loss of the tuber angle and decided valgus deformity.

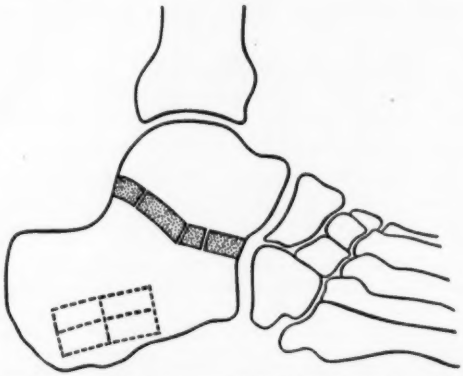

Fig. 5.—Recommended method for comminuted fractures with decided valgus deformity. The subastragalar joint is exposed through a lateral incision, and the loose fragments are denuded of their articular cartilage and replaced. Large chips then are removed from the posterolateral aspect of the os calcis and placed in the lateral portion of the joint to fill the open space and correct the valgus deformity. If the calcaneocuboid joint has been damaged, it and also the astragaloscaphoid joint should be fused at the same time.

The main fragments are replaced and their articular surfaces bitten off with rongeurs, and then blocks of cancellous bone are removed from the lateral surface of the heel and placed in the joint space to correct the valgus deformity.

C. For fractures which extend also into the calcaneocuboid joint a triple arthrodesis as recommended by Conn is indicated; this includes the subastragalar, calcaneocuboid and astragaloscaphoid joints.

After operation plaster is applied, including the pin if restoration of the tuber angle has been necessary, and immobilization continued for eight weeks. Finally, a walking cast is applied with the foot in the equinus position, and weight bearing is encouraged; the walking cast usually is discarded by the twelfth week, when the fusion has become solid. Experience with such treatment has been satisfactory. Fusion has occurred in every case, and there has been no permanent pain in the injured part.

TABLE 2.—*Fractures of Os Calcis Involving Articular Surface (Arthrodesis)*

Total number of fractures		27
Average age of patients		47.7 yr.
Average time from operation to reemployment		6.1 mo.
Average permanent disability rating for former work		11.0%
Final results	Good (19 cases)	70.0%
	Fair (8 cases)	30.0%
	Poor (0 cases)	0%

The results of 27 consecutive comminuted fractures involving joint surfaces which have been treated and observed by the writer since 1942 are given in table 2.

A good result indicates that the patient returned to work without pain and with little or no disability, a fair result indicates ability to walk with some discomfort but inability to return to regular work and a poor result indicates severe pain and complete disability. This series comprised the more severe form of injury; in several instances both heels were involved. Most of the patients were employed at light or heavy occupations, although the group included a clergyman, a housewife and a banker. Five of the patients were not operated on until several months after injury, with consequent delay in recovery. Many of them had decided atrophy of the leg muscles, with corresponding weakness for long-continued walking and for climbing stairs.

SUMMARY

Selective treatment for comminuted fractures of the os calcis is described, sharply differentiating those which do not involve articular surface and those which do. The results of 50 consecutive cases are tabulated to illustrate these two types.

Fractures which did not involve the articular surface and were not displaced were treated with early, protected weight bearing in a walking cast. Comminuted fractures were reduced by Hermann's method of reshaping. In 20 of 23 cases there was little or no permanent disability.

The comminuted fractures which involved articular surfaces were treated routinely by means of early arthrodesis and correction of deformity, and thus the permanent pain and disability which are anticipated in all such injuries were minimized. Those with decided displacement and compression deformity were treated with a combination of early arthrodesis through a lateral exposure and packing with cancellous bone chips; in 19 of 27 cases the results were good. The average time from injury to reemployment was 6.1 months. There was an average permanent disability rating of 11 per cent.

It should be emphasized that many of the injuries which are reported in this paper occurred in nonindustrial cases; a series of industrial workers with similar injuries might have a higher percentage of disability.

TREATMENT OF MIXED TUMORS OF THE PAROTID GLAND BY SUBTOTAL PAROTIDECTOMY

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SURGICAL operation on the parotid gland is most often performed to remove a mixed tumor. The major technical problem involved is related to the proximity of the gland to the facial nerve. The major oncologic problem is the correlation of the histologic picture of the tumor with the ultimate prognosis. This paper will be limited to the technical problems involved in the treatment except when a technic may influence the possibility of subsequent recurrence. The surgical procedure described is not original but is not as well known as is desirable.

DEFINITION OF SUBTOTAL PAROTIDECTOMY

Total removal of a gland implies that each cell of that organ has been removed. Anatomically, the parotid gland has several prolongations which make total removal difficult. The anatomy of these areas has been best described by Bailey [1] and by McCormack and others.[2] The parotid gland has extensions (1) along the anterior-inferior wall of the external auditory canal, (2) along the posterior border of the ascending ramus of the mandible, and thence to the lateral pharyngeal wall, and (3) along the inferior border of the zygoma. While these prolongations may frequently be removed in subtotal parotidectomy, the margin of excision is so slim that no claim should be made to total removal of all parotid cells. For this reason, it is preferable to refer to the procedure as subtotal rather than total parotidectomy and to reserve the latter for block removal of the gland without preservation of the facial nerve.

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1. Bailey, H.: Treatment of Tumors of Parotid Gland with Special Reference to Total Parotidectomy, Brit. J. Surg. **28**:337, 1941; Parotidectomy: Indications and Results, Brit. M. J. **1**:404, 1947.

2. McCormack, L. J.; Cauldwell, E. W., and Anson, B. J.: The Surgical Anatomy of the Facial Nerve, with Special Reference to the Parotid Gland, Surg., Gynec. & Obst. **80**:620, 1945.

ANATOMY

Description of the surgical anatomy of the parotid gland is always closely correlated with that of the anatomy of the facial nerve. While these have been carefully described in individual articles over a period of years, the information has been neither accurately recorded in some standard textbooks nor widely disseminated. For this reason a short review of the pertinent information is advisable.

McWhorter [3] described the relationship of the facial nerve to the parotid gland as follows:

> The facial nerve and its main branches lie between the superficial and deep lobe of the parotid gland. These lobes are not united at their upper extremity. The two lobes are united in H shape, the connecting isthmus corresponding to the crossbar. Upon approaching the isthmus of the gland from behind, the facial nerve divides into its superficial division which passes forward above the isthmus and its lower division which passes below the isthmus. The uppermost and the lowermost facial branches may not come into contact with the deep lobe (on account of its small size) though still under cover of the superficial lobe of the parotid. The facial nerve lies between the two lobes, sometimes enfolded in grooves on the opposing surfaces.

McCormack and others [2] studied one hundred preserved specimens. Like McWhorter, they found that the facial nerve "lying between two lobes of the parotid, partially separates the gland into a large superficial and a small deep portion, the two parts being connected by a slender isthmus which passes beneath the two diverging portions of the nerve." They demonstrated clearly that the nerve does not go through the substance of the parotid gland.

Certain surgeons have stressed this relationship and have recorded accurate clinical anatomic descriptions.[4] However, many common sources of reference have not been so accurate. A recent textbook of surgery [5] states that the "lower anterior surface of the parotid is crossed by the spreading branches of the facial nerves." Another standard textbook on anatomy [6] states that "on emerging from the stylomastoid foramen, the facial nerve runs forward in the substance of the parotid

3. McWhorter, G. L.: The Relations of the Superficial and Deep Lobes of the Parotid Gland to the Ducts and to the Facial Nerve, Anat. Rec. **12**:149, 1917.

4. Janes, R. M.: Surgical Treatment of Tumors of Salivary Glands, S. Clin. North America **23**:1429, 1943. Sistrunk, W. E.: Tumor of Parotid Gland, S. Clin. North America **1**:1515, 1921. Adson, A. W., and Ott, W. O.: Preservation of Facial Nerve in Radical Treatment of Parotid Tumors, Arch. Surg. **6**:739 (May) 1923. Marshall, S. F., and Miles, G. O.: Tumors of Submaxillary and Parotid Gland Areas, S. Clin. North America **501**:515, 1947. Bailey.[1]

5. Homans, J.: A Textbook of Surgery, Springfield, Ill., Charles C Thomas, Publisher, 1945, p. 599.

6. Gray, H.: Anatomy of the Human Body, edited by Warren H. Lewis, ed. 24, Philadelphia, Lea & Febiger, 1942, p. 920.

gland." It is little wonder that many physicians feel that permanent injury to the facial nerve is unavoidable if the major portion of the parotid gland is to be removed.

PREOPERATIVE PREPARATION

In each case elicitation of a complete history and physical examination are carried out. A sialogram may be done by the method of Blady and others.[7] This yields some information on the size and position of the tumor in relation to the remainder of the parotid gland and a reasonably accurate estimate of whether the tumor is benign or malignant. We have not obtained a sialogram in each case. No biopsy is obtained. The diagnosis is made on the clinical history and the physical findings alone.

Many patients with a parotid tumor already know of the possibility of facial nerve injury in relation to surgical treatment and are aware of the nature of the subsequent disfigurement which could result. Therefore it is extremely important that the surgeon explain to the patient that it is possible to remove the tumor and gland without dividing the facial nerve so long as the tumor is a benign one and has not invaded the adjacent facial nerve. It is also well to inform the patient that even when the nerve has not been cut there may be a temporary loss of facial motion of about two months' duration. (In our experience with more than 25 individual cases there has been no permanent loss of function of the facial nerve except when the nerve has been deliberately divided because of invasion by cancer. There has been some temporary loss of function in 100 per cent of these patients, initially complete in about 50 per cent. Recovery has been satisfactory within an average of two months.)

ANESTHESIA

General anesthesia is the one of choice. This assures excellent exposure and complete freedom from extraneous motion. Intratracheal intubation is necessary to assure adequate airway at all times. Beyond this, the actual anesthetic agent is a matter of individual decision in each case. It is possible to perform these operations under local anesthesia, if absolutely necessary.

OPERATIVE PROCEDURE

A Y-shaped incision is made (fig. 1). The anterior limb is placed in the groove between the anterior surface of the external ear and the skin of the face, extending from the tragus down to the tip of the lobe

7. Blady, J. V., and Hocker, A. F.: Sialography: Its Technique and Application in Roentgen Study of Neoplasms of Parotid Gland, Surg., Gynec. & Obst. **67**:777, 1938.

of the ear. The posterior limb of the Y is placed in the groove between the external ear and the mastoid process, again extending from the level of the tragus to the tip of the lobe. The lobe of the ear is now elevated up to the floor of the external auditory canal and held there by a traction suture. This exposes a triangular area. The stem of the Y is now made by continuing the incision downward from the lobe of the ear and curving forward along anatomic skin lines about 3 cm. below and parallel to the horizontal ramus of the mandible. This incision is carried through the platysma muscle of the neck. The posterior skin flap is elevated in that plane to uncover the anterior half of the sternocleidomastoid muscle.

The anterior edge of the sternocleidomastoid muscle is now separated from the posterior border of the parotid gland, and dissection is carried

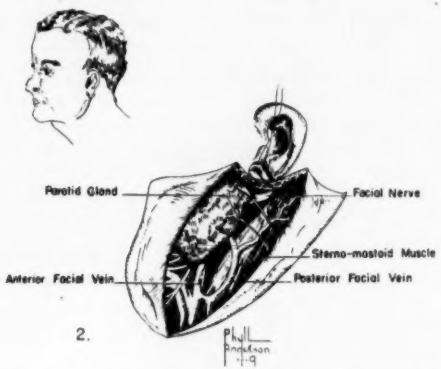

Fig. 1.—*1*, incision for subtotal parotidectomy; *2*, initial exposure of facial nerve.

down along its anterior border in this plane. As long as the dissection follows the anterior border of the sternocleidomastoid muscle, it is impossible to injure the facial nerve. Dissection is continued to a depth of about 1.5 cm. This is the region in which the facial nerve will be found (fig. 1) as it emerges from behind the mastoid process deep to the muscle and curves beneath the external auditory canal to gain access to the anterior surface of the mandible. This region is a cube measuring not more than 1 cm. on any edge. Here, the nerve is at least 3 mm. in diameter and cannot readily be divided by any careful surgeon who uses ordinary means of hemostasis. No further steps in removal of the parotid gland should be undertaken until the nerve has been identified.

After the facial nerve has been identified, it is traced forward by elevating the posterior border of the parotid gland from the nerve itself.

As the dissection proceeds beyond the posterior border of the ascending ramus of the mandible, the facial nerve is found to divide into its two main branches between which passes the isthmus of the parotid gland, connecting the superficial and deep lobes (fig. 2).

The superficial lobe of the parotid gland is then freed from the inferior main division of the facial nerve and its three terminal branches (cervical, mandibular and buccal) (fig. 2). These nerve branches will usually remain attached to the anterior surface of the masseter muscle, from which the lobe can readily be elevated. Occasionally the parotid lobe will extend around the posterior border of the ascending ramus of the mandible. Such an extension can be elevated and removed when present, but complete removal may be rather difficult if the prolongation is sufficiently long to extend to the lateral surface of the pharyngeal wall. In these circumstances, a portion of the gland is allowed to remain unless the indications for its complete removal are definite.

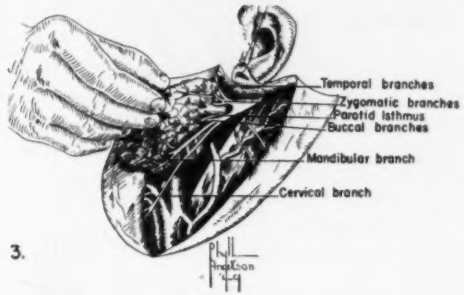

Fig. 2.—*3*, exposure of the main branches of the facial nerve and the isthmus of the parotid gland.

The superior of the two main branches of the facial nerve can now be followed forward by elevating that portion of the superficial parotid lobe lying cephalad to the parotid isthmus. This dissection exposes the three branches (temporal, malar and infraorbital) into which the superior branch of the nerve divides (fig. 2). A process of the superficial lobe will often be found to extend along the anterior wall of the external auditory canal. This can be removed if necessary but is usually allowed to remain unless the indications for its removal are definite.

The entire superficial lobe of the parotid gland has now been separated from all branches of the facial nerve but remains attached by the isthmus to the deep lobe, by Stensen's duct to the buccal mucosa and by its anterior surface to the overlying skin of the face. The facial nerve is completely exposed. The gland is now separated from the overlying skin in the plane or subcutaneous tissue, with no chance of injury to the terminal branches of the facial nerve.

Dissection is continued along Stensen's duct, the terminal branches of the facial nerve being kept in view at all times. Stensen's duct can be followed across the anterior border of the masseter muscle into the fat pad of the cheek, where it can be clamped, cut and ligated. If necessary, the duct can be divided flush with the mucous membrane of the buccal mucosa or, if this is not definitely indicated, it can merely be ligated and divided at the anterior border of the masseter muscle.

The superficial lobe of the parotid gland is now attached only by the isthmus which connects it to the deep lobe (fig. 2). This isthmus passes

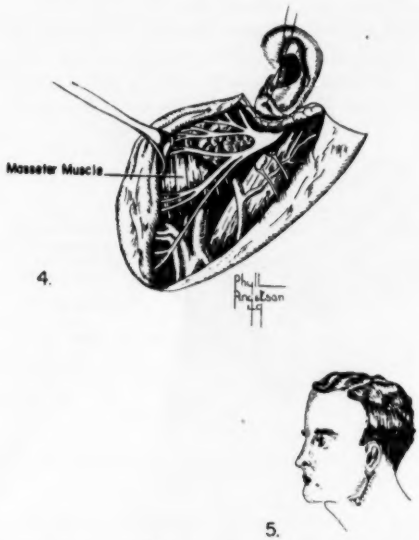

Fig. 3.—*4*, complete exposure of facial nerve after removal of superficial lobe of parotid gland. The deep lobe and isthmus can be removed by retracting the overlying nerve fibers. *5*, closure of incision.

between the two main branches of the facial nerve. These two main branches can now be retracted as necessary and the deep lobe of the parotid separated from the anterior surface of the masseter muscle. Occasionally a deep lobe will not be present. At times the tumor will be in such a position that it is not necessary to consider removal of the deep lobe. However, it is always necessary to keep the facial nerve and its branches in view at all times as the small terminal branches of the nerve frequently anastomose anterior to the isthmus of the parotid gland and can inadvertently be cut if not clearly exposed.

After the entire parotid gland has been removed, the facial nerve and all its branches are clearly visualized in the base of the wound (fig. 3). Hemostasis is completed. The skin is closed with interrupted fine silk sutures, a small drain is placed in the lower angle of the incision and a pressure dressing is applied.

POSTOPERATIVE CARE

The patient has fully recovered within twenty-four hours. As there is usually a temporary partial loss of facial motion on the side operated on, the eye on that side should be protected from foreign bodies by the use of eyeglasses. Although the patient is instructed to apply massive hot wet soaks to the operative site and to massage paralyzed facial muscle, it is not certain that these procedures are of any real benefit.

The drain is removed within twenty-four hours, and the skin sutures are removed within seven days. Local induration within the wound reaches a maximum in two weeks and has completely disappeared in eight weeks. Facial paralysis, when present, completely clears within twelve weeks.

GENERAL COMMENT

Mixed tumors of the parotid gland have shown an incidence of recurrence after surgical removal varying from 18[8] to 33 per cent.[9] Recurrence of a mixed tumor must be due either to continued growth of residual tumor cells not removed at first operation or to the development of a new tumor. Although the first alternative is supported by the best evidence, it is obvious that a subtotal parotidectomy would be a more effective preventative measure than would be mere enucleation of the tumor in either instance.

Certain illustrative cases have been assembled to prove individual points in this regard.

A. *Residual Tumor Remaining After an Inadequate Operation Can Develop into Clinically Demonstrable Tumor.*—This is shown in case 1.

CASE 1.—A 20 year old white youth gave a history of having had a nodule appear below and behind the lobe of the right ear at the age of 13. Two years later his family physician had advised removal of the nodule and had attempted this as an office procedure with the patient under local anesthesia. The physician soon realized that he was dealing with something other than a "sebaceous cyst." However, he proceeded to curet tumor material from within the capsule and suture the operative incision. He informed the patient that the tumor would undoubtedly recur and require further treatment. It was not until three years later that the

8. Sistrunk, W. E.: Mixed Tumors of Parotid Gland: Operative Treatment, in Collected Papers of the Mayo Clinic, Philadelphia, W. B. Saunders Company, 1921, vol. 13, p. 861.

9. Wood, F. C.: Mixed Tumors of Salivary Glands, Ann. Surg. **39**:57 and 207, 1904.

patient noted the presence of several nodules in the scar of the previous incision. These nodules grew slowly. He was finally admitted to the military hospital. A subtotal parotidectomy was done, the facial nerve being preserved and the scar of the previous operation excised together with all surrounding nodules in one mass. On gross examination of the excised specimen there were numerous separated tumor nodules. Several of these were within the scar but outside the limits of the parotid gland. Microscopic examination of the nodules confirmed the diagnosis of mixed tumor.

This case represents growth of both residual tumor within the parotid gland and of tumor implanted into the tissues surrounding the gland. It exemplifies the ease with which implants grow. It has been shown that in each of 7 collected cases in which the original mixed tumor had been treated by curettage there was recurrence of the tumor.[10]

B. *Enucleation of a Mixed Tumor Which Seems Microscopically Complete May Leave Residual Tumor Cells in Surrounding Parotid Tissue.*—Case 2 is an example of this type.

CASE 2.—A 30 year old white man first noted a nodule anterior to the lobe of the right ear about three years prior to initial treatment. At the time of treatment the nodule was removed by enucleation with the patient under local anesthesia. The surgeon's notes state that "it was completely excised without rupture of the capsule." The pathologist's description of the excised tumor states that the tumor was "apparently completely excised."

Because of our feeling regarding the treatment of these mixed tumors and because there was some question of its absolute benignity although no tumor was clinically evident, a subtotal parotidectomy was done, with excision of the previous scar. Examination of the gross specimen showed no tumor, but microscopic examination of that portion of the parotid in close proximity to the scar of the previous operation disclosed several small areas of tumor.

It is apparent that neither the surgeon nor the pathologist can be certain of the completeness of an enucleation by gross examination. While it is not possible to predict that each residual tumor area would have developed into a clinically demonstrable tumor, it is reasonable to assume this. This inference is again borne out by the finding of a recurrence rate of 50 per cent following enucleation of a mixed tumor, compared with that of 13 per cent following excision of the tumor with a margin of parotid tissue.[10]

C. *Tumor Cells Can Be Identified Within the Capsule of the Mixed Tumor.*—An example of this type is case 3.

CASE 3.—A 55 year old Negro woman noted a lump in the right parotid area eleven years prior to her entry to the hospital in July 1947. On examination, a mass measuring 5 cm. in diameter was present beneath the lobe of the right ear. Facial movements were normal. On Jan. 3, 1948, she consented to a subtotal

10. Stein, I., and Geschickter, C. F.: Tumors of Parotid Gland, Arch. Surg. **28**:492 (March) 1934.

parotidectomy. Examination of the gross specimen showed the tumor to be well encapsulated. On microscopic examination the tumor was considered benign, but cells were found within the structure of the capsule itself.

Treatment of a parotid tumor by simple enucleation is based on the premise that the tumor is surrounded by a covering of fibrous tissue cells which separate it from the surrounding parotid gland. It is not possible to say through which microscopic layer of capsular cells surgical enucleation will occur. When tumor cells occur within the capsule, as in the case just described, it is certainly possible that some of these may be left behind within those layers of the capsule which remain. It then follows that some of these remaining cells may grow into demonstrable tumors.

D. *Early Malignant Change in a Mixed Tumor May Be Controlled by Initial Wide Excision.*—It is not feasible to differentiate a benign tumor from one showing early histologic malignant change if clinical criteria alone are employed. One can assume that certain cases will occur in which early malignant change is associated with minimal invasion of adjacent normal parotid tissue. If such tumors are excised with an adequate margin through normal parotid tissue it is possible that clinical cures may be obtained. This is suggested by certain clinical reports.[1] Our cases are too recent and too few to be of significance. This type of case is being collected for subsequent evaluation.

Case 4.—A 32 year old man noted a lump beneath the lobe of the left ear for years prior to treatment. This had grown slowly until it was roughly 3 cm. in diameter. The mass showed no clinical evidence of invasion of surrounding structures. Facial movements were normal. A sialogram was consistent with the diagnosis of a benign tumor. A subtotal parotidectomy was performed, the facial nerve being preserved. At no time during the procedure was tumor visualized or broken into. Grossly, the tumor was encapsulated. Microscopically it showed invasion through the capsule into surrounding parotid tissue. Histologic examination of the surrounding tissue up to the line of excision had not been made. As the gross specimen was not preserved, further study was not possible. Wider surgical removal would have required sacrifice of the facial nerve. The patient, an active trial lawyer, decided against such a procedure although it was recommended. Up to now, two years after treatment, he has had no demonstrable recurrence, and he has normal facial movements.

It seems logical that the recurrences of mixed tumors of the parotid gland treated by subtotal parotidectomy should be limited to those tumors which lie so close to a vital (i. e., the facial nerve) or irremovable structure that an adequate margin of surrounding normal tissue cannot be excised. The tumor cells left behind in the vital structure (i. e., the nerve sheath) will be the source of the recurrence. Routine sacrifice of the facial nerve is not indicated to prevent this.

CONCLUSIONS

Subtotal parotidectomy is the procedure of choice in surgical treatment of mixed tumors of parotid gland origin. This is borne out by statistics obtained from the literature. Enucleation of the tumor has been shown to result in incomplete removal in at least one specific instance. Residual tumor cells have been shown to be capable of forming additional clinically demonstrable tumors. This is the probable cause of most recurrences.

Subtotal parotidectomy is a safe procedure. The only complication which has acted as a deterrent to its more universal use has been fear of injury to the facial nerve. This can be prevented by careful exposure of the nerve during the surgical procedure. One method of accomplishing this has been presented. Most of the differences of opinion and some of the poor results have been due to lack of understanding of the anatomy of the facial nerve, although this knowledge has been in the medical literature for years.

SUMMARY

The procedure of subtotal parotidectomy has been described. Reasons for its routine use in surgical therapy of mixed tumors are stated, and examples are furnished.

MANAGEMENT OF BLEEDING PEPTIC ULCER

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DURING the past two decades the treatment of bleeding peptic ulcer has been evolutionized. Its seriousness and high toll of life have been better appreciated. Multiple variations of treatment have arisen, attesting in their multiplicity alone to the difficulties and disappointments attendant on the treatment of the massively bleeding peptic ulcer. This report is concerned with cases of bleeding peptic ulcer encountered at this hospital from October 1946 through October 1948. During this period 347 patients with peptic ulcer were treated, 115, or 33 per cent, of whom had gross bleeding. Gross bleeding is defined as demonstrable hematemesis or melena on the patient's admission to the hospital or within forty-eight hours previous to his admission. The amount of bleeding varied from a minor hemorrhage lasting only a day or two, with no change in the hematologic picture, to rapid, repeated, massive hemorrhages leading to exsanguination and death despite multiple transfusions.

It is felt that the rational management of a patient with a bleeding peptic ulcer requires close cooperation between physician and surgeon. Consequently a medicosurgical team has followed these patients from their admission to the hospital through their entire course of treatment. They were admitted to the medical service, and hematologic studies including a complete blood count, determination of hematocrit, bleeding and clotting times and nonprotein nitrogen levels were done on their admission. On evaluation of the physical and laboratory picture, therapy was begun, consisting of sedation as indicated and hourly feedings of milk and aluminum hydroxide. Blood replacement was carried out as needed, often in two or more extremities at once. When severe blood

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

depletion existed, the hematologic studies mentioned were repeated at frequent intervals. A continuous clinical chart was kept of the blood pressure, pulse and general response. Immediate surgical intervention was undertaken if the patient continued to bleed profusely and required repeated massive transfusions or had not responded well within the first twenty-four hours. A good response was indicated by a cessation of hematemesis and melena, by return toward normal of the pulse and blood pressure and by stabilization of the general hematologic picture. If the patient recovered but had had numerous previous episodes of bleeding despite an adequate medical regimen, he was carefully evaluated for elective gastrectomy.

In practice, no effort was made to classify the patients into groups on their admission or to define treatment by classification. Rather, each was followed individually by the combined team of internist and surgeon and treatment evolved on an hour by hour basis. Factors such as duration of bleeding, former treatment, age and rapidity of bleeding were taken into consideration in the treatment of each case.

For statistical and follow-up purposes the patients were placed in three groups. Group 1 are those whose bleeding was of a minor nature. Although gross bleeding occurred, patients in this group did not present a picture of blood loss either clinically or on laboratory examinations. The red blood cell counts were not below 4,000,000 per cubic millimeter, the hematocrit values were not reduced and pulse and blood pressure were normal. In group 2 are those who had had considerable bleeding, with changes in the blood picture. Many had clinical evidences of shock on their admission. However, all patients in this group had shown a good and prompt response to active medical treatment in that clinical and laboratory signs returned to normal. A certain percentage of these patients, group IIa, underwent elective surgical procedures after recovery from the acute episode. In group III are those patients who did not respond to energetic medical therapy and who seemed to face death unless surgery were undertaken.

A statistical review of the total series of 115 patients is shown in table 1. Since there is an occasional reference in the literature to the seasonal incidence of ulcer exacerbations, a notation has been made on the season of admission. No conclusions in this regard are warranted in the series under discussion.

GROUP I

Group I is made up of 37 patients who were treated conservatively and without blood replacement. Twenty-two were bleeding for the first time, and 15 had bled previously. Only 5 were above the age of 45. All 37 had a definite history of ulcer, the average duration being six years. None was considered to have been on a satisfactory ulcer regimen,

although many had recourse to occasional antacids or milk to relieve pain. Seventeen used alcohol excessively. During hospitalization 4 of these patients had a normal gastrointestinal roentgenogram, 19 showed a definite ulcer crater and 14 a duodenal deformity. Five had had previous complications of ulcer other than bleeding; of these, 4 had perforating ulcer. All patients showed a prompt remission of symptoms on active treatment and were discharged on a medical regimen.

GROUP II

There are 64 patients in group II. There was a wide discrepancy in the total blood loss in various persons of this group, but their consideration and treatment were similar. Ten required no blood transfusions although on their admission the erythrocyte counts were between 3,500,000 and 3,800,000 per cubic millimeter. Others received from 500

TABLE 1.—*Data on 115 Patients with Bleeding Peptic Ulcer*

Group	Total	Dec. to Feb.	March to May	June to Aug.	Sept. to Nov.	Above 45	Below 45	First Bleeding	Recurrent Bleeding	Previous History of Ulcer	On Diet	Excess Alcohol	Gastrointestinal Roentgenograms: Ulcer Crater	Deformed Bulb	Normal	Not Done
I	37	11	7	11	8	5	32	22	15	37	0	17	19	14	4	0
II	64	18	13	17	16	15	49	36	28	61	13	22	28	33	5	0
III	14	2	3	3	6	7	7	7	7	12	0	4	0	0	0	14
Total	115	31	23	31	30	27	88	65	50	110	13	43	45	47	9	14
IIa	19	5	3	3	8	7	12	2	17	19	5	6	8	11	0	0

to 8,500 cc. of whole blood, the average amount being 2,500 cc. Almost without exception these persons showed a good immediate response to supportive treatment, and it was felt that surgical intervention could be safely deferred.

Sixty-one patients in this group had a definite history of ulcer. The average duration of symptoms was 5.4 years. Only 15 were 45 years of age or over. Thirty-six were bleeding for the first time, while 28 had had previous gastrointestinal bleeding. Fifty-one were not on an adequate medical regimen, and 22 indulged in alcohol to excess. On roentgenographic study 25 showed a duodenal ulcer crater, 33 a deformed duodenal bulb and 1 a gastric ulcer. In 5 the gastrointestinal roentgenogram was normal. Eight had had previous complications, including perforation in 5 instances.

GROUP IIa

Group IIa consists of 19 patients, or 30 per cent of group II, who underwent an elective surgical procedure to prevent further bleeding. In each case the patient was in good chemical balance and nutritional state

at the time of operation, which was done under optimal conditions. Eighteen had had previous multiple bleeding episodes, while 1 had marked pyloric obstruction and had bled for the first time. There had been no bleeding for a period varying from one week to a month prior to surgical intervention. All 19 patients had a definite history of ulcer. Seven of the 19 were older than 45 years of age. Fourteen had not followed a diet, and 6 were addicted to alcohol. Roentgenographic studies showed a duodenal crater in 8, a duodenal deformity in 10 and a gastric ulcer in 1. A Hoffmeister gastrectomy was usually performed. There were no operative deaths in this series. Fourteen patients had an uneventful recovery and 5 had postoperative complications as indicated in table 2. The ulcer was removed in 5 instances. One patient underwent gastroenterostomy, which has proved to be inadequate as the patient has

TABLE 2.—*Postoperative Complications*

Group IIa	19 patients	0 Deaths
		14 No complications
		1 Shock at beginning procedure, no operation, recovery
		2 Subcutaneous hematoma
		1 Stomal edema
		1 Atelectasis, thrombophlebitis, pulmonary embolus
Group III	12 patients	4 No complications
		1 Death, pulmonary edema
		1 Death, continued bleeding
		2 Atelectasis
		1 Wound infection
		2 Wound disruptions
		1 Bile drainage

continued to have intermittent episodes of bleeding. Another had severe hypertensive cardiovascular disease and went into collapse as the peritoneal cavity was opened. The abdomen was closed without further surgical intervention, and he recovered uneventfully.

GROUP III

Group III is made up of 14 patients who bled so rapidly and so massively that replacement therapy seemed inadequate. Immediate surgical intervention appeared to be the alternative to a fatality. Two died without undergoing operation. No bleeding point was found in 1 patient who underwent an exploratory laparotomy and gastrotomy, with recovery. One patient was subjected to a subtotal gastric resection, with a presumptive diagnosis of bleeding duodenal ulcer, but later investigation revealed a bleeding polyp of the colon. Ten underwent gastric resection for bleeding ulcer, with 2 deaths. The operative mortality was

16.6 per cent in 12 cases, or 20 per cent in 10 cases in which gastrectomy was performed for massive hemorrhage from peptic ulcer.

The incidence of postoperative complications was high in this group, only 4 having recovered without complications. Table 2 indicates the complications incurred. It appeared that most of these patients would have died without surgical intervention. This would have given a mortality rate of about 10 per cent for the 115 patients.

Each of these patients was treated energetically by medical means and massive blood replacement for periods varying from four to forty-eight hours. Either they responded not at all or poorly or, if they responded, they continued to show evidence of massive active bleeding. This was evidenced by continued melena and hematemesis, clinical shock and poor response of the laboratory blood picture.

The 2 patients who did not receive surgical treatment are presented here in detail (cases 1 and 2). Three of the operative cases in this group are also presented (cases 3, 4 and 5).

CASE 1.—J. W. B., a 21 year old white man with a previously demonstrated duodenal ulcer, was admitted to the hospital after four days of severe gastrointestinal bleeding. He was in shock, with 1,850,000 red blood cells per cubic millimeter. He was given 7,000 cc. of whole blood and 4,000 cc. of electrolytes before he died, thirty-two hours after his admission. He did not recover from peripherovascular collapse. Necropsy revealed pulmonary edema and bilateral pleural effusion.

Comment.—This patient received inadequate blood replacement during the first four days of his terminal episode, and then, after that length of time, pulmonary edema occurred after massive blood replacement. However, too much fluid in the form of electrolytes was given. Disastrous results from excessive fluid and blood replacement seem much more likely when bleeding with unrelieved shock has occurred during a number of days previously. It is noted that digitalization was of no aid in this instance. This case illustrates that it is possible for young persons to have exsanguinating hemorrhage from peptic ulcer.

CASE 2.—A. E., a 50 year old white man with a previously demonstrated duodenal ulcer, was admitted to the hospital four days after the onset of severe melena and hematemesis. He was in shock, with 1,910,000 red blood cells per cubic millimeter. During the next sixty-two hours he received 24,500 cc. of whole blood but did not respond. Necropsy revealed moderate pulmonary edema and the pancreaticoduodenal artery eroded through in the floor of the ulcer (figure).

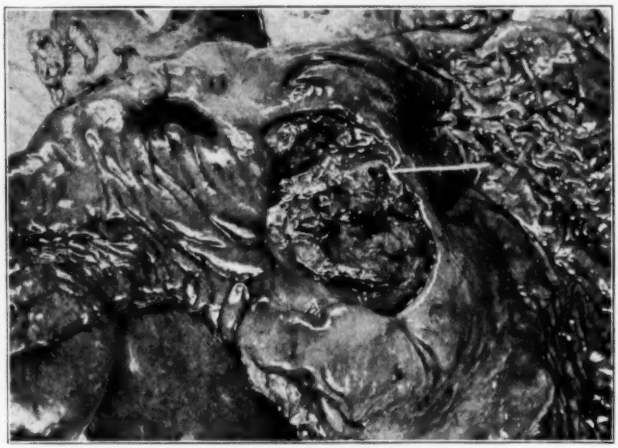
Comment.—This case illustrates irreversible shock from bleeding ulcer despite massive replacement of blood. There was no alternative to continuous and vigorous blood replacement. The postmortem findings demonstrated generalized passive congestion, including pulmonary edema, which is prone to occur in such instances.

CASE 3.—E. R. M., a 23 year old white man, was admitted to the hospital five days after the onset of severe gastrointestinal bleeding. Despite transfusions previous to his admission, he was in mild shock, with a red blood cell count of 2,640,000 per cubic millimeter. He was given 1,500 cc. of whole blood and 2,000 cc. of electrolytes. A subtotal gastrectomy was performed, but the bleeding point was

found in the fundus too late to preclude the resection of the distal stomach. It was controlled by ligature. Postoperatively he did well until 1,000 cc. of whole blood was given. He then died, and pulmonary edema was confirmed at necropsy.

Comment.—Exsanguinating hemorrhage may occur from an ulcer involving the fundus of the stomach. It was evident that the patient had undergone an unnecessary gastrectomy. Perhaps the correct diagnosis could have been made from a preoperative gastrointestinal roentgenogram. Certainly the operative approach would have been modified had a preliminary gastrotomy been carried out. It is believed that all patients who do not have a proved ulcer should have the benefit of this preliminary operative step, which does not greatly increase the operating time or add appreciably to the morbidity of the procedure.

Of 10,750 cc. of fluid given intravenously in thirteen hours, 2,500 cc. was electrolytes, which might have been better eliminated. The patient had bled to such



The arrow indicates the open lumen of a 3 mm. artery in the base of a large chronic gastric ulcer found in case 2. A duodenal ulcer may be seen to the left.

a point previous to his admission that adequate blood loss could not be made up rapidly. However, all but the last 1,000 cc. of blood was considered necessary to carry the patient through the operation. That 1,000 cc. seemed to precipitate pulmonary edema. Digitalization might have been of value.

Case 4.—A. W. D., a 49 year old white male alcoholic addict with a previously demonstrated duodenal ulcer, was admitted to the hospital three days after the onset of severe gastrointestinal bleeding. He was in mild shock, with a red blood cell count of 3,200,000 per cubic millimeter. He responded to transfusions promptly, but on the third day in the hospital bleeding began once more. A subtotal gastrectomy was immediately performed. The ulcer was not removed. On the first postoperative day the patient bled to death.

Necropsy revealed the pancreaticoduodenal artery eroded in the ulcer bed.

Comment.—This case was handled satisfactorily in all but one respect; i. e., the ulcer was not removed at operation. In retrospect, removal seems to have been possible. At the time, however, it was felt that mechanical and chemical rest of the ulcer would be sufficient to control bleeding and that the added time and trauma incident to the removal of the ulcer would outweigh the advantage of its extirpation. The outcome of the case proved the fallacy of this therapy and bore out the observation of others that large arteries such as the pancreaticoduodenal and the right gastric artery must be controlled directly for success in this procedure.

CASE 5.—A. Q. R., a 57 year old white alcoholic with a history of ulcer, was admitted to the hospital thirty-six hours after the onset of melena. His erythrocyte count was 2,950,000 per cubic millimeter. A barium swallow revealed no esophageal varices, and the duodenal cap appeared normal. The melena continued. There was no hemoptysis. The patient was often in shock despite massive replacement of blood. After five days he consented to surgical intervention. At operation there was no blood in the upper part of the gastrointestinal tract, but gastrectomy was performed. No ulcer was seen or felt. Later a bleeding sigmoid polyp was demonstrated and removed.

Comment.—This case was most instructive, and in retrospect the mistake seems more obvious than it was at the time. The absence of hematemesis during the entire episode, the hint given by the barium swallow, the stomach and small bowel free of blood at operation all should have indicated the seat of the pathologic process. No pathologic condition was felt in the colon. Undoubtedly a gastrotomy would have precluded the gastrectomy and consequently would have been of great aid in the proper treatment of the patient.

In this group the ulcer was removed in 4 patients and left in situ in 6, 1 of whom bled to death soon after operation. Twelve of the group had a previous history indicating ulcer. Four were alcoholic addicts. Seven had bled on previous occasions, while 7 were bleeding for the first time. Among the 10 patients who underwent gastrectomy for peptic ulcer there was considerable variation in the duration of preoperative bleeding. Five were operated on within forty-eight hours, 2 after four days, 1 after five days and 2 after six days from the onset of hemorrhage. Seven were below 45 years of age. None was on an adequate ulcer regimen. A preoperative series of gastrointestinal roentgenograms was not done in any of these cases. An average of 9,500 cc. of whole blood was given. The average red blood cell count on the patients' admission was 2,900,000 per cubic millimeter. The ages of the 2 patients who died without undergoing operation were 21 and 50 years and of the 2 who died after operation 23 and 49 years.

FOLLOW-UP

The follow-up of the 25 living patients of group IIa and group III who have undergone gastrectomy for bleeding peptic ulcer is not completely satisfactory because of the inadequate postoperative time factor, which runs from two years to three months. However, 15 patients have had good results, that is, they have regained their normal weights, are working and have no gastrointestinal complaints. Five are considered

to have fair results, in that they are working but have various gastrointestinal complaints and do not feel as well as previously. In these 5 there have been no recurrences of bleeding. The result in 4 is considered to be a failure, 1 having had recurrent bleeding. Three of these 4 are alcoholic addicts and have required multiple hospitalizations for malnutrition. One has not been followed up.

COMMENT

The management of patients with minimal and moderate bleeding presents no real problem. Small differences in technic and refinements of method probably have little influence on the patient's recovery as long as the blood volume is replenished and the patient is carried henceforth on an adequate ulcer regimen. This is far from the case in the small group of patients who do not respond promptly to conservative measures. It is about this group that the real problem of correct treatment centers. What procedures should be taken in the extremely ill person to establish the diagnosis before surgical intervention? What methods are to be used to determine the extent of bleeding and whether or not the bleeding is continuing? Is there a means to prognosticate the eventual outcome in the individual case whether operation is undertaken or not? How much blood should the patients receive and how fast should it be given? Should they be subjected to a difficult and lengthy operative procedure? If so, what type and how extensive should it be?

Crohn and others [1] have shown that the diagnosis in these cases is not always clear. They illustrated the fact that the bleeding point may be difficult or impossible to find even at laparotomy or necropsy. The extreme condition of some patients tends to limit the diagnostic procedures applicable. Among others, Schatzki [2] and Hampton [3] have advocated preoperative gastrointestinal roentgenograms with no manipulation. They have stressed their safety and desirability. Heuer [4] was in disagreement and cited 3 deaths attributable to preoperative roentgenographic studies. In the present series preoperative roentgenographic diagnosis has not been used routinely for fear of precipitating further hemorrhage. In some instances a gastrotomy has been done

1. Crohn, B. B.; Marschak, R. H., and Galinsky, D.: Repeated Gastro-Duodenal Hemorrhages Without Discoverable Explanation, Gastroenterology **10**:120-128 (Jan.) 1948.

2. Schatzki, R.: Roentgenologic Examination in Patients with Bleeding from Gastrointestinal Tract, New England J. Med. **235**:783-786 (Nov. 28) 1946.

3. Hampton, A. O.: A Safe Method for the Roentgen Demonstration of Bleeding Duodenal Ulcers, Am. J. Roentgenol. **38**:565-570 (Oct.) 1937.

4. Heuer, G. J.: Surgical Aspects of Hemorrhage from Peptic Ulcer, New England J. Med. **235**:777-783 (Nov. 28) 1946.

to insure location of the bleeding point. That step is felt to be of great importance in cases in which the diagnosis of peptic ulcer has not been proved by a recent roentgenogram.

Ingegno,[5] Christiansen[6] and, more recently, Amendola[7] have held that the nonprotein nitrogen level of the blood is an indicator of prognosis and of continued bleeding. An increased or rising nonprotein nitrogen level indicates further bleeding. In the present series nonprotein nitrogen levels were determined at intervals in 24 patients, and no significant clinical correlation with the amount of blood loss was noted. The patients were all well hydrated during treatment, and it was felt that this played an important part in keeping the nonprotein nitrogen at normal levels.

Heuer[4] has pointed out the importance of the pathologic changes caused by the ulcers. Nearly always in the fatal cases large vessels such as the right gastric or the pancreaticoduodenal artery have been eroded. Sometimes the vessel is eroded only through its side and is unable to contract. This contention is supported in the present series, for 3 of the 4 patients who died had erosion of the pancreaticoduodenal artery.

It seems that the study of the hematocrit value, hemoglobin and red blood cell count at intervals, coupled with the observation of the patient's general appearance, pulse, respiration and blood pressure, furnishes an adequate index to the extent of bleeding. In this series no patient who was bleeding severely and actively failed to have frequent hematemeses and melena. It was not difficult to tell if a patient was bleeding or to estimate how rapidly he was bleeding, but it was most difficult to predict if he was going to continue to bleed despite therapy. Allen and his colleagues[8] and others[9] have emphasized that age plays a most important part and have shown that bleeding in patients over 50 years of age has a more serious prognosis than bleeding in the

5. Ingegno, A. P.: The Elevated Blood Urea of Acute Gastro-Intestinal Hemorrhage and Its Significance, Am. J. M. Sc. **190**:770-774 (Dec.) 1935.

6. Christiansen, T.: Uraemia as Cause of Death in Massive Haemorrhage from Peptic Ulcer, Acta med. Scandinav. **85**:333-345, 1935.

7. Amendola, F. H.: The Management of Massive Gastroduodenal Hemorrhage, Ann. Surg. **129**:47-56 (Jan.) 1949.

8. Allen, A. W.: Bleeding Duodenal Ulcer, New England J. Med. **208**:237-241 (Feb. 2) 1933. Allen, A. W., and Welch, C. E.: Subtotal Gastrectomy for Duodenal Ulcer, Ann. Surg. **124**:688-707 (Oct.) 1946. Allen, A. W., and Benedict, E. B.: Acute Massive Haemorrhage from Duodenal Ulcer, Ann. Surg. **98**:736-749 (Oct.) 1933.

9. (*a*) Lahey, F. H., and Marshall, S. F.: The Surgical Treatment of Peptic Ulcer Based upon 130 Subtotal Gastrectomies for Peptic Ulcer, New England J. Med. **217**:933-940 (Dec. 9) 1937. (*b*) Moore, F. D.: Current Practices in the Surgical Treatment of Ulcer, S. Clin. North America **27**:1071-1087, 1947.

younger group. In this series it has been found that the age factor has not been of as great significance as stressed elsewhere. Of the 4 deaths, 2 have been in patients of 21 and 23 years of age. Of the 14 patients considered for emergency surgical treatment, 7 were under 45 years of age. It seems apparent that young persons may bleed rapidly to death from this disease as well as those in middle age. Each patient should be handled as an individual problem.

When massive bleeding has been inadequately treated for a long period, shock may be irreversible and vigorous attempts to restore the circulatory system to normal may precipitate pulmonary edema, as demonstrated in case 2. In instances in which pulmonary edema is a calculated risk, there seems to be no choice other than continuous massive transfusions in an attempt to bring the circulatory system to normal. In patients with prolonged bleeding who do respond to efforts to correct the circulatory blood volume, evaluation of the blood loss should be made and replacement therapy should be limited to an amount necessary to replace that which is lost and to maintain circulatory stability. It is felt that parenteral administration of fluid and electrolytes is indicated only in the initial period while blood is being cross matched because of the danger of overloading a circulatory system that has suffered an acute loss of blood and will receive replacement in large amounts. Frequent observation of the patient and determination of the hematocrit value and red blood cell count are essential when massive replacement therapy is in progress. Digitalis may be helpful for some patients of this group.

There are wide variations in opinion concerning what form the active treatment is to take. Meulengracht [10] felt that surgical intervention has little or no place in the treatment of bleeding ulcer and reported a corrected mortality rate of 1.5 per cent in 1,031 cases without operation. Since 1887, when Miculitz [11] first attempted to control hemorrhage by operation, surgeons [12] have advocated intervention, but

10. Meulengracht, E.: The Medical Treatment of Peptic Ulcer and Its Complications, Brit. M. J. **2**:321-324 (Aug. 12) 1939; Fifteen Years' Experience with Free Feeding of Patients with Bleeding Peptic Ulcer, Arch. Int. Med. **80**:697-708 (Dec.) 1947.

11. Cited by Nielsen, N. A.: About the Choice Between Medical and Surgical Treatment of Ulcus Ventriculi S. Duodeni, Acta chir. Scandinav. **55**:105-127, 1922.

12. (*a*) Lewisohn, R.: Partial Gastrectomy for Bleeding Duodenal Ulcer, Ann. Surg. **102**:142-143 (July) 1935. (*b*) Balfour, D. C.: The Surgical Treatment of Haemorrhagic Duodenal Ulcer, ibid. **96**:581-587 (Oct.) 1932. (*c*) Pfeiffer, D. B.: Massive Hemorrhage from Posterior Duodenal Ulcer, ibid. **103**: 473-477 (March) 1936. (*d*) Westermann, J. J.: Surgical Aspects of Bleeding Gastric and Duodenal Ulcer, ibid. **101**:1377-1388 (June) 1935. (*e*) Lahey and Marshall.[9a] (*f*) Moore.[9b]

with varied enthusiasm. Finsterer [13] has been the foremost pioneer in this work and for thirty years has stressed early gastrectomy in all cases of bleeding ulcers. Stewart and others [14] have more recently advocated early surgical treatment for all patients admitted to the hospital with a red blood cell count of 2,500,000 or less. Dunphy and Hoerr [15] base their decisions on the rate of bleeding as the most important factor and emphasize that if the patient bleeds more than 500 cc. every eight hours surgical intervention is indicated. On the basis of the experience in the present series, if the patient fails to respond within a few hours to rapid, massive replacement of blood or if the response is difficult to maintain because of continued bleeding, emergency treatment is in order. In the event that the patient remains in deep shock, little can be done other than continued replacement of blood. In this series only those who were in shock for a period of days failed to respond. Surgical treatment has not been attempted unless the patient has shown some ability to respond to blood replacement.

Heuer [4] has emphasized early operation, within twenty-four to forty-eight hours or not at all, since the patients become so debilitated after that time that adequate replacement of blood is usually not possible. He has shown a mortality rate of 70 per cent in operations done after forty-eight hours of the onset of bleeding in contrast to 10 per cent with early operation. We are convinced that early surgical intervention is a key to success in these cases, but from this series it is evident that operation should not be denied a patient on the basis of long duration of bleeding. If the patient can be prepared by replacement therapy as evidenced by reasonably stable pulse and blood pressure, an attempt should be made to control the hemorrhage. Of the 10 patients in this series who were operated on, 2 had bled six days, 1 five days and 2 four days preoperatively. Both of the postoperative deaths were in persons who had been bleeding for a period exceeding forty-eight hours.

Most authors [16] agree that gastrectomy is the procedure of choice. Heuer [4] has emphasized the necessity of actually removing the ulcer itself at operation. Mechanical and chemical rest as furnished by a gastrectomy without removal of the ulcer is not enough to guarantee

13. Finsterer, H.: Surgical Treatment of Acute Profuse Gastric Hemorrhages, Surg., Gynec. & Obst. **69**:291-298 (Aug.) 1939; Operative Treatment of Severe Gastric Haemorrhage of Ulcer Origin: A Reply to Critics, Lancet **2**:303-305 (Aug. 8) 1936.

14. Stewart, J. D.; Schaer, S. M.; Potter, W. H., and Massover, A. J.: Management of Massively Bleeding Peptic Ulcer, Ann. Surg. **128**:791-802 (Oct.) 1948.

15. Dunphy, J. E., and Hoerr, S. O.: Indications for Emergency Operation in Severe Hemorrhage from Duodenal Ulcer, Surgery **24**:231-238 (Aug.) 1948.

16. Lahey and Marshall.[9a] Balfour.[12b] Westermann.[12d]

control of the bleeding when such an artery as the pancreaticoduodenal has been eroded in the ulcer base. Although in this series the ulcer was not in every instance removed at operation, it is felt that removal is of the utmost importance in gastrectomies done as an emergency procedure, even at some additional hazard to the patient. One death in this series was due to continued bleeding from the unremoved duodenal ulcer.

SUMMARY

One hundred and fifteen cases of bleeding peptic ulcer have been presented and their management outlined. In the series reported, the incidence and the serious import of massive exsanguinating hemorrhage were as great in the younger age group as in patients over 45 years of age.

CONCLUSIONS

1. The treatment of massive bleeding from the upper part of the gastrointestinal tract is a combined medicosurgical problem requiring the constant attention of both internist and surgeon. Each case is an individual problem and must be managed as such.

2. Replacement of blood should be continued until the patient responds, despite the risk of overtransfusion and resultant pulmonary edema.

3. Early intervention when surgical treatment is indicated offers the best chance of success with the massively bleeding patient, but no time limit should be set.

4. Subtotal gastrectomy is often a lifesaving procedure in cases in which bleeding cannot be controlled by active medical means. The gastrectomy should include the source of bleeding. Gastrotomy is a valuable adjunct to exploratory laparotomy in cases in which the diagnosis of peptic ulcer may be doubtful.

5. Arterial transfusions and digitalization may be valuable adjuncts to the armamentarium.

LOCAL AND SYSTEMIC EFFECTS OF HEAT AND COLD IN RATS

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TEMPERATURE is one of the most powerful governors of life processes, since it affects nervous and circulatory functions, membrane permeability, gaseous dissociation and other external determinants of the oxygenation and nutrition of cells and also the action and coordination of enzymes and all other physical and chemical processes within cells. Numerous researches have only slightly illuminated this vast subject; also it is improbable that many laws can be found which are universally applicable to lower and higher, poikilothermic and homoiothermic, thermophilic and cold resistant organisms. In experiments on mammals, especially from a practical viewpoint, there is often insufficient regard for the considerable differences in thermal reactions between man and all the common laboratory species, and few investigators show any awareness of the contrasts between the reactions of the whole body, of parts normally connected with the body and of parts isolated from the body.[1] One law is actually universal, namely, that every thermal effect is the product of temperature and time. For micro-organisms there is routine information of the acute thermal death point and the milder temperature which kills them in a definite longer time. The acute death point is known for several tissues of some higher animals, but nothing is established concerning their time tolerance for smaller deviations from normal. Intermediate alterations are also undetermined; for example, the physical therapists judge their treatments empirically, and they seem never to have investigated the possible consequences if their customary brief time limits should be exceeded. This paper calls attention to the existence of the theoretic and practical problem and undertakes a preliminary inquiry into some time relations of low and high temperatures, including the rapidity of transitions between them.

From the City Hospital, Welfare Island, N. Y.

1. Allen, F. M.: Canad. M. A. J. **51**:220-226, 1944; Clinics **4**:1642-1674, 1946.

METHODS

Rats' tails were chosen as the regular test object, with a few comparative observations of other parts. The advantages are the convenience of keeping a rat comfortable in an individual holder, while the tail is exposed to a selected temperature to which it conforms more quickly and closely (as we have verified by thermocouple readings) than is possible with most other species or other parts of the body. Disadvantages are the allowances to be made for different thermal reactions of rat and man, the tenuous blood suppply through long narrow vessels which favors the maintenance of a fixed temperature and at the same time creates a special vulnerability and, on the other hand, the theoretic possibility that the tail may have an exceptional temperature

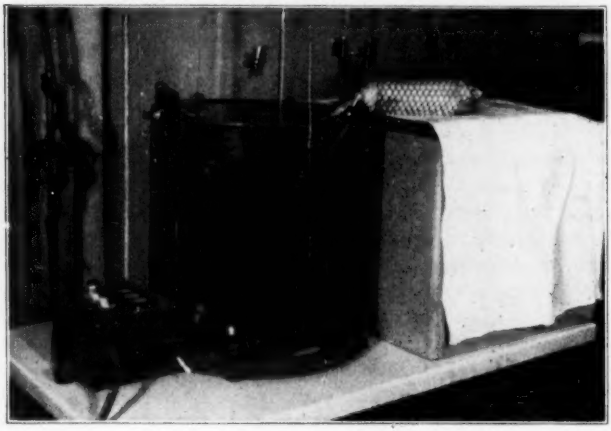

Fig. 1.—One form of immersion experiment, with tail nearly vertical in bottle in constant temperature bath.

tolerance to adapt it to the wide fluctuations to which it must be subject in winter and summer weather. A greater handicap was the limitation of our facilities which necessitated using immersion in water as the means of adjusting temperature, inasmuch as wetness so seriously complicates the influence of temperature.[2] Trials with an impervious coating of the tails were unsuccessful. A special apparatus supplied by the Therm-O-Rite Products Corporation of Buffalo, N. Y., was not sufficiently ventilated to prevent condensation of moisture. Wetness due to condensation may likewise be assumed in Greene's [3] closed chamber

2. Footnotes 1 and 5.

3. Greene, R.: Lancet **2**:695-697, 1942.

cooled with carbon dioxide ice or when rats' tails [4] or rabbits' feet [5] are inserted in rubber covers. From a practical standpoint, our necessity could be converted into an advantage, because the clinical treatment of burns and most other surgical lesions deals with wet surfaces. Thus the combination of moisture and temperature is a clinical problem, and theoretic interpretations must take account of the two factors.

The microscopic examinations merely supplemented the gross observations. The purpose was clinical rather than histologic, and usually the simple necrosis or survival of the tail was the decisive feature. All determinations were repeated in multiple series to assure uniformity. Since the form of experiment is so simple, the results can be compressed into the briefest possible summaries, with a few records of illustrative experiments.

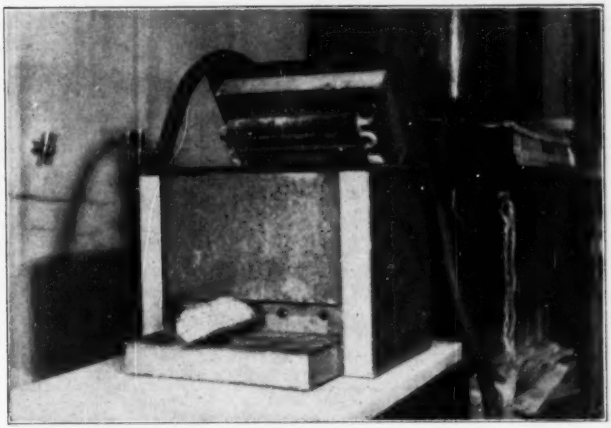

Fig. 2.—Rat with tail passed horizontally through hole into Therm-O-Rite cold air chamber. Four holes on this side and four on opposite side provide for 8 rats simultaneously. The cover is tilted to show metal fins, which are chilled to a selected degree by fluid circulated through the heavy rubber tubes.

I. *Chilling of Rats' Tails.*—In conformity with the "immersion foot" experiments of previous writers, continuous immersion of the tails in water at 40 F. (5 C.) for two days causes edema and apparent hyperemia. Edema increases with successive days, but about the third day the blood becomes darker and hyperemia appears only after warming. Up to this point there is only the temporary anesthesia of cold, and the

4. Brooks, B., and Duncan, G. W.: Ann. Surg. **112**:130-137, 1940.

5. Quintanilla, R.; Krusen, F. H., and Essex, H. E.: Am. J. Physiol. **149**:149-161, 1947.

tail is sensitive on warming; but with the fourth day diminished sensitiveness is evident even after warming and corresponding degeneration of nerves is seen microscopically. The outcome is illustrated in the following eight day experiment.

On removal from the water after eight days the tail appeared swollen and slightly congested. About 3 cm. was clipped from the end for microscopic examination, which showed the characteristic edema, engorged vessels and nerve degeneration. After the rat was caged for a few hours in a warm room the tail was more swollen and excitement indicated pain in spite of the extensive degeneration of nerves. The next morning the tail was dusky, with pale and reddish mottling. There was no longer evidence of pain either spontaneously or when another short segment was amputated. The microscopic picture was one of advanced degeneration. On the following day the tail was dark

TABLE 1.—*Rats' Tails in Water at Reduced Temperatures*

No. of Rats	Water Temperature	Time, Days	Results
6	46 to 56 F. (8 to 13 C.)	2 or 3	Slight to moderate edema and congestion; amputation painless while cold; cut surface bleeds freely, warmth restores sensation
8	Same	4 or 5	Increase of gross changes; nerve degeneration microscopically; cyanosis and absence of sensation after warming
9	Same	6 or 7	Previous changes intensified; pallor followed by deeper cyanosis; sometimes progressing to necrosis of end of tail
10	Same	8 or 9	Extreme edema and degeneration; tail sometimes immediately necrotic; sometimes dark scanty blood flow followed by necrosis
8	Same	10	Complete pale necrosis and maceration of all tails

and obviously necrotic. It mummified rapidly, and within five days the entire chilled portion was lost.

This is the extreme grade of "immersion foot," for beyond this, on the ninth or tenth day in the cold water, all the tails are found white, flaccid, bloodless and completely necrotic.

Table 1 illustrates the closely similar results at slightly higher temperatures. The graded groupings in regard to both temperature and time are explained as follows. The equipment did not maintain rigidly accurate temperatures but allowed fluctuations of 2 to 4 degrees even under the best conditions. Furthermore, without special stirring, there is apt to be a distinct temperature difference in the water at the top and bottom of the tube containing the tail. Regardless of these factors, there are gradations of results between individual animals side by side subjected to identical temperatures for identical times. The results were not perceptibly different in more laxly managed experiments, in which the temperatures at different times might range most of the way between the stated extremes (46 to 56 F. [8 to 13 C.]). These and the

previously mentioned observations display a general similarity of the effects of cold and wetness, with no more than slight graded differences in the range from 40 to 56 F. (5 to 13 C.). As mentioned later, when the temperature rises to a level of "moderate" coolness, near 70 F. (21 C.), the injury becomes much less. The main point is the graded character of the effects and the absence of any sharp change at 10 C. (50 F.), which recent authors have tended to emphasize as the critical temperature for hemoglobin dissociation.

Rats as a rule readily survive the loss of their tails by necrosis or otherwise, and this rule holds true in these experiments. Death occurs in only one way. At any time, early or late in the experiments and without regard to the state of the tail, a single animal may show a difference from the others in refusing to eat. In proportion to the degree of depression the rectal temperature is found low, perhaps 15 or 20 F. below normal. Such an animal can be saved only by stopping the experiment and warming artificially. No reason is known for this exceptional hypothermia in contrast to that in other animals in the same series.

A few comparative tests were performed by chilling the lower part of one hindleg. Because of the difficulties of maintaining immersion without obstruction of circulation or wetting of the body, these experiments were not continued beyond two days. It was ascertained that the "immersion foot" changes occur more rapidly and markedly in the foot than in the tail. They illustrated the previously mentioned fact [1] that the violence of the reaction is an important factor in addition to mere tissue temperature.

II. *Influence of Tourniquet.*—The beneficial suppression of nervous and vascular reactions by a tourniquet must be balanced against the harm of lack of circulation. Each tail, immersed at 40 F. as before, had a narrow rubber band applied near the base, which was replaced every six or eight hours with a new one located slightly more distally to avoid thrombosis from continuous pressure. Time is the determining factor, for within certain limits the tails are better preserved and less edematous, but later the nutritive lack becomes fatal. Brooks and Duncan,[4] with the blood excluded by fluid pressure instead of a tourniquet and without actual immersion, obtained survival of the tails after ninety-six hours of refrigeration, though with some degree of subsequent sclerosis. In the present immersion experiments no tail survived the four day limit. The following experiment is illustrative.

After four days in water at 40 F., a ligated tail showed no swelling or other gross change. The sites of the successive tourniquets remained visible as pink grooves. A 3 cm. segment was clipped from the end shortly after removal of the last tourniquet. There was no sign of sensation, and no bleeding beyond one small drop of dark blood. After one hour in a warm atmosphere, active hemorrhage required ligation of

the tail tip. After a few more hours, swelling and hyperemia were similar to those in tails without a tourniquet, but without signs of pain or tenderness. In the following days the swelling increased and the color gradually became darker, progressing from the tip. The end result was necrosis and loss not of the entire tail but up to a sharp demarcation about the middle of the tourniquet zone. In other words, the tissues which had undergone the least asphyxia, as created by the first few tourniquet applications, survived. Notwithstanding recent suppositions regarding membrane permeability and oxygen dissociation, it is obvious that the minimal tissue metabolism receives support from the feeble blood circulation in the rat's tail at 5 C.

III. *Controls for Water, Temperature and Position.*—Results were essentially the same when Ringer's solution was substituted for water, indicating that osmosis was not a decisive factor in the edema and other changes.

Tails were also immersed in water at temperatures between 60 and 80 F., mostly about 70 F. The effects of wetness at these moderate temperatures were comparatively trivial, and no tails suffered permanent damage or were lost. In contrast to the necrosis at 40 F., ten days of immersion at 70 F. made no gross change except maceration of the epidermis. There was evidently normal sensation when a 3 cm. segment was clipped from the end. The active bleeding indicated slight hyperemia. The microscopic changes were only slight edema and scattered small subepithelial hemorrhages. There was a more marked inflammatory reaction in the twenty-four hours following removal from the water. These results suggest that greater harm could follow longer immersion, and they thus agree with clinical reports of conditions resembling "immersion foot" among survivors of shipwreck in tropical seas.

It is obvious, as previously pointed out,[6] that when experiments introduce such grossly disturbing factors as pressure (Brooks and Duncan) or forced dependent position plus immersion (Large and Heinbecker [7]), the interpretation of the effects as due merely to low temperature is unfounded and false. The tails in our experiments were subjected to no pressure, and no differences were noticed to result from different freedom of movement in a roomy tube, a larger bottle or a large reservoir. While it is doubtful if a movable tail suffers from dependency like a leg, our immersion experiments compared vertical positions of the tail with a more customary angle of about 45 degrees, and the previously mentioned Therm-O-Rite apparatus provided a flat horizontal position. All possible complications were thus excluded except the important one of wetness.

6. Allen, F. M.: Arch. Phys. Med. **26**:92-98, 1945; Acute Arterial Injuries, Correspondence, J. A. M. A. **140**:974 (July 16) 1949.

7. Large, A., and Heinbecker, P.: Ann. Surg. **120**:707-749, 1944.

For control of this factor, there is fortunately one published experience with dry cooling. Baxter and More [8] kept normal tails of rats in dry air at 52 F. (11 C.) for periods of seven to fourteen days. Gross changes were not evident, but microscopically there were found slight shrinkage and irregularity of nuclei, slight changes in the collagen bundles of the dermis and relaxed and dilated appearance of large and small arteries and veins, with dense packing and clumping of red cells in them. Other tails after scalding survived temperatures as low as 44 F. (7 C.) for fourteen days. The described slight changes after dry cooling could presumably become more severe with longer duration. On the other hand, rats have been experimentally acclimated to air at 44 F. (7 C.) for as long as thirty days,[9] and they are likewise known to adapt themselves so as to thrive indefinitely in commercial cold storage plants, without losing their tails. It can only be questioned whether the partial immobilization in Baxter and More's experiments could account for the slight histologic changes in the tails.

IV. *Warming in Water.*—A rat's tail kept three and a half hours in water at 110 F. (43 C.) shows no important injury, particularly no impairment of sensation or motion. This resistance of nerves invites passing notice. As will be mentioned hereafter, a lower temperature of the entire body kills a rat almost instantly. The assumption that the central nervous system is the vulnerable point has been verified when we have killed rats by heating the exposed medulla with water at this temperature. We have frequently referred to the similar difference in resistance to low temperature. All peripheral parts and some of the viscera can withstand brief freezing; but even momentary freezing of the brain or heart is fatal to all vertebrates and most invertebrates, and no animal of higher rank than the hibernators is known to survive a body temperature below 56 F. (13 C.). Since anoxia is now often correlated with thermal injuries, the comparison may be extended to it. The fatal limit of anoxia of the central nervous system is known to be only a very few minutes. In former experiments [10] it was found that the abundant ganglion cells scattered through the pancreas can withstand anoxia as well as the parenchyma, namely, for more than an hour. Surgeons perhaps seldom reflect that stoppage of blood flow to any part of the gastrointestinal tract, by accidental causes or operative clamping, might make fatal disturbances if the rich plexuses and ganglions were not able to withstand anoxia up to several hours. In order to survive the ordinary vicissitudes of life, it is essential that the ganglions throughout the body shall be more resistant than the central nervous cells to heat, cold and anoxia, and in general they seem fully as resistant as the structures amid which they are located.

8. Baxter, H., and More, R. H.: Ann. Surg. **125**:177-193, 1947.
9. Adolph, E. F.: Am. J. Physiol. **155**:378-387, 1948.
10. Allen, F. M.: J. Metabolic Research **1**:165-192, 1922.

It is only surprising that the difference should be so extreme between nerve cells which appear so closely similar anatomically, while there is a similarity of resistance to the muscular or visceral cells which are radically different both in structure and in embryonic origin. Still other differences may be noticed between the neurone bodies and their neuraxes. For example, the motor fibers in ligated limbs show far greater resistance to anoxia than their parent cells in the spinal cord but far less resistance than the muscles and other surrounding structures.[11] Also an abdominal tourniquet applied for one to several hours causes sensory, motor and vasomotor paralysis, which passes off after weeks.[12] Here the spinal cord is preserved by the intraspinal circulation; but unless the posterior root ganglions are also thus nourished,

TABLE 2.—*Rats' Tails in Water at Elevated Temperatures*

No. of Rats	Water Temperature	Time, Days	Results
5	107 to 108 F. (41.5 to 42 C.)	1	Tails swollen and red; no necrosis
7	Same	1½	Greater swelling; necrosis of distal parts of 3 tails; 1 rat died after 2 days
6	Same	2	Tails swollen, insensitive, flaccid; dark bleeding on section near base, none near end; partial or complete necrosis of all tails; 1 rat died during experiment, 3 after 1 or 2 days; 2 survived with loss of tail
4	109 to 110 F. (42.5 to 43 C.)	1	Necrosis of all tails; 1 rat survived, 3 died
2	103 to 104 F. (39.5 to 40 C.)	2	Slight edema and congestion; sensation present; cut surface bleeds freely
5	Same	3	Increased edema and congestion; some cyanosis toward tip
4	Same	4	Marked edema; deeper venous congestion; necrosis of distal parts of 2 tails within 24 hours after removal from water
4	Same	5	Marked edema and cyanosis; loss of sensation; later necrosis of all or part of every tail; 2 rats died
5	Same	6	Edema and pale necrosis of all tails; 2 rats died during experiment, 2 others within 24 hours; 1 survived with loss of tail

they must share the high resistance of the sympathetic ganglions, while the nerve fibers of all kinds first degenerate and then regenerate. There seems to be adaptation partly anatomically, according to liability to accidents, and partly teleologically, since there is greater necessity of preserving the nerve cells which cannot regenerate than the fibers which can regenerate. While these distinctions have both theoretic and practical importance for accidental or operative conditions involving tissue asphyxia, no studies have been made of the differences in thermal resistance illustrated in these experiments.

The time factor in thermal action is seen when baths at 107 to 110 F. (41.5 to 43 C.), which feel only mildly warm to an observer's hand, cause necrosis of rats' tails within one or two days (table 2).

11. Allen, F. M.: Ann. Surg. **108**:1088-1093, 1938.
12. Allen, F. M.: Am. J. Surg. **55**:451-466, 1942.

Still milder temperatures of 103 to 104 F. (39.4 to 40 C.), which are within the febrile range which the human body may tolerate for days or weeks, cause necrosis of the tails within six days, preceded by the edema and degenerative changes characteristic of "immersion foot." The contrast between the nonfatal experiments with cold and the high mortality with warmth is easily explained by the fact that intoxication from both tissue autolysis and bacterial action is inhibited by low and promoted by high temperature. The most striking fact is that the lesions, which are traditionally linked in the medical mind with cold and wetness, are produced more rapidly and severely by moderate warmth and wetness.

The physiologic mechanism needs further investigation. The edema following either burning or freezing is clearly due to vascular injury, the protein content of the exudate being sufficient proof in itself. All authors have followed Lewis in assuming that the swelling after more moderate cold is due to increased capillary permeability, except Lange,[13] who interprets it as reduced resorption. This harmonizes with the general rule[14] that membrane permeability increases with higher and decreases with lower temperature, and the edema from moderate overheating would be logically explained by increased permeability. But the reduced permeability which Lange found in cooled rabbit skin was not duplicated in the vessels of the mesentery and intestine, which fact illustrated the lack of uniformity in biologic reactions. The question appears to be open whether the mechanism of edema is different at different temperatures, whether there is a reversal of the direction of permeability or whether there is a common factor even for moderate heat and cold, namely capillary injury creating edema by the same abnormal process in both instances.

V. *Dry Heating.*—Dry air at about 120 F. is tolerated by the human skin even more easily than water at such temperatures, because of the slighter heat conduction. We made approximately a dozen preliminary tests with rats' tails inserted through small openings into an electric oven. For technical reasons these experiments were carried only far enough to show the general consequences. An initial arterial hyperemia soon changed to venous engorgement. Failing circulation hastened the approximation of the internal temperature of the tail, as measured by the thermocopule, to the surrounding air temperature, so that only two to five hours at temperatures from 115 to 125 F. (46 to 51.5 C.) sufficed to bring on total necrosis. Effects are notoriously different when tissues (either animal or human) with a deficient blood supply are thus heated through and through than when an ample circu-

13. Lange, K.: Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **5**:154-162, 1943.

14. Brown, E., and Landis, E. M.: Am. J. Physiol. **149**:302-315, 1947.

latory reaction keeps the actual tissue temperature little changed. Clinically, burns from moderate heating of areas with deficient circulation are familiar, while physical therapists use heat chiefly for the reactive influence.

Since the rat's tail is so well adapted for maintaining altered tissue temperatures, the question arose whether a slight elevation above the general body temperature would result in sustained hyperemia, either directly or through the stimulus of metabolic products, and whether hypertrophy might ensue. Tests were undertaken by confining growing rats a few weeks old in individual holders, with their tails subjected to constant oven temperatures of 102 to 105 F. (39 to 40.5 C.). These experiments were not continued beyond two weeks, partly because of technical difficulties but chiefly because no temperature was found to maintain arterial hyperemia. The rat's tail is capable of considerable and prolonged red active hyperemia, as seen in inflammation from various causes. But the simple elevations in temperature soon resulted in appearances of passive venous congestion, with some edema. In the higher temperature scale a deepening of color toward the tip of the tail threatened necrosis if there were longer continuance. Any possibility of hypertrophy was obviously precluded. The interpretation seems to be that a slight elevation above the normal temperature in any organ is not beneficial, but on the contrary the slight excess continued sufficiently long can be as destructive as a brief duration of excessively high temperature.

VI. *Alterations of Local Temperature.*—These nonfreezing experiments obviously do not touch the question of slow or rapid warming after freezing. The practical application is rather to contrast baths, which are used empirically for reactive stimulation, though there has never been an investigation of alternations of actual tissue temperature as illustrated in the following experiments.

1. With the animal under anesthesia produced by pentobarbital sodium, one hindleg of a rat was kept immersed in ice water for three and a half hours, then changed abruptly to water at 110 F. (43 C.), in which it remained three and a half hours. Immediately after its removal, the thermocouple temperature in the calf muscles was 104 F. (40 C.). The foot was bright pink and moderately swollen. It returned to normal within the next few days, without blistering or other signs of a burn from the sudden elevation of temperature by about 70 F. The effect was no greater than that in the legs of controls which were heated without preliminary chilling. In other words, a burn does not result from a rapid transition between tolerated extremes of temperature.

2. The same procedure applied to tails gave final thermocouple readings of 107 to 108 F. (41.5 to 42 C.). There was correspondingly

greater edema, venous stasis and sometimes necrosis of the terminal 2 or 3 cm. There was no consistent difference between tails heated with and without preliminary chilling.

3. The entire hindquarters were immersed in ice water for fifteen minutes and then changed suddenly to water at either 110 or 115 F. (43 or 46 C.), and these alternations were repeated for fifteen periods of fifteen minutes each. The rectal temperatures fluctuated rapidly between about 70 and 100 F. (21 and 38 C.). The resulting inflammatory appearances were greatly reduced by the next morning, when the entire program was repeated. Numerous rats then died overnight, without blistering and with moderate inflammatory edema. Since thermal effects are always a product of temperature and time and lesions designated as burns may result either from brief intense heat or from long contact of a water bottle at more moderate temperature, it is conceivable that a condition equivalent to burn shock may follow a sufficient continuance of a temperature which is ordinarily regarded as nonburning. The survivors showed a sharp contrast between the red feet and the limp and bluish tails. The latter were lost by necrosis. The feet remained red and swollen, and the legs were nearly paralyzed, presumably from degeneration of nerves. In different individuals the legs either returned slowly to normal or were lost because of progressive gangrene.

4. A similar program of alternations between ice water and room air resulted in slight "immersion foot" changes, as would be expected. Systemic chilling predominated, however, and many rats died from cold.

5. In similar alternations between room air and water at 110 or 115 F. (43 or 46 C.), the rapid cooling in air still made an abrupt change in temperature. The results were identical with those in experiment 3, showing that the wider temperature range created by the ice water played no part.

6. Several other series were tried, with fifteen alternations between ice water and the warm water, each of only ten or five minutes' duration. Here rapidity of alternations was emphasized at the price of reduced individual and total time periods. The effects were correspondingly diminished, again showing that the mere speed or extent of temperature change was not a governing factor.

VII. *Systemic Temperatures.*—It has been mentioned elsewhere that the rat tolerates a much more severe acute reduction of body temperature than man but is greatly inferior in tolerance of prolonged hypothermia. For hyperthermia its endurance is much less than that of man, in both degree and time. The relatively short times for which rats can withstand heating to body temperatures of 103 to 105 F. (39.5

to 40.5 C.) are well known to investigators. The acute heat tolerance of man is not precisely established and doubtless may vary with a number of internal and external conditions. Records of recovery from very brief elevations as high at 112 F. (44.4 C.) appear to be authentic, but reports of recovery from temperatures running as high as 115 F. (46 C.) are improbable. We have heated rats by confinement in a dry air oven and more often by immersing vertically to the shoulders in water. A deep colon temperature of 108 F. (42 C.) is quickly fatal, perhaps within one minute, and death occurs instantly with a rise to 109 F. (42.7 C.). Time factors and chances of resuscitation are present at intermediate levels (much more at low than at high temperatures), but instant and absolute death is the result of overstepping the critical limit in either direction, namely, the upper limit of 109 F. (42.7 C.) and the lower limit of 56 F. (13 C.). Though the figures for man are different, there is good reason to believe that the limits are just as absolute, and this danger should deter anybody from taking risks in human tests.

There is less precise definition of the time factor which causes death at various milder temperatures if they are sufficiently long continued. A distinction must still be made between absolute death, such as was mentioned, and a state of near death or apparent death in which heart beat and respiration may be scarcely perceptible or may actually stop. The possibility or impossibility of recovery is decided not merely by the absolute degree of high or low temperature (as long as the fatal limits are not exceeded) but also by the time factor, reflex reactions, exhaustion, shock and heart failure. Cardiac irregularity is commonly described in human subjects before a fatally low temperature is reached. According to Ungley's report [15] from the Dachau concentration camp records, "In general death occurred at body temperatures between 24 and 26 C. (about 76 to 79 F.) and in seven recorded instances after periods of 53 to 106 minutes." But Fay,[16] avoiding shock and excitement and using sedatives to inhibit defense reactions, maintained temperatures of this order safely for much longer periods, and he also reduced the body temperature as low as 74 F. without fatality.

Though it is admittedly desirable to reduce the body temperature rapidly in hyperpyrexia or heat stroke, there is dispute concerning rapid or slow rewarming after chilling. Fay considered that the time limit of "hibernation" of human subjects was fixed by the degeneration which was found in cardiac muscle fibers. He attributed this to relative overwork, because the human heart does not slow its rate in propor-

15. Ungley, C. C.: Report on Visit to Occupied Europe (British Admiralty), 1945.

16. Fay, T.: New York State J. Med. **40**:1351-1354, 1940. Smith, L. W., and Fay, T.: Am. J. Clin. Path. **10**:1-11, 1940. Smith, L. W.: Ann. Int. Med. **17**:618-636, 1942.

tion to the temperature, as do the hearts of true hibernators. The rat and other common laboratory animals do reduce their heart action practically like the hibernators, and though they escape cardiac degeneration they die within a day or two from the same temperatures which the human subject tolerates for a week. As the survival bears a rough relation to the size and strength, the deaths must be attributed chiefly to exhaustion, and the closest reproduction of human conditions will doubtless be furnished by some larger species, such as the hog. For the reasons explained, Fay was a leading advocate of gradual rewarming after chilling, for fear of heart failure. His unique experience warrants acceptance of his judgment in cases in which the body has adjusted itself to prolonged hypothermia. In cases of more acute hypothermia the advisability of speedy rewarming is beyond doubt. The previously quoted report by Ungley stated: "The most effective therapeutic measure was rapid rewarming. Rewarming must be rapid to cushion the 'after-drop' in temperature, which continues to fall for 10 to 15 minutes after the subject is removed from the cold water. . . . In three extreme cases a bath in hot water at 50 C. was successful even though heart and respiration were at a standstill." We can fully confirm this statement for rats, cats and dogs which are nearly dead after chilling for a few minutes to a few hours. They often die from the delay involved in slow warming. The maximum saving of life is obtained with the quickest possible warming in a water bath or oven considerably above normal body temperature, and there is never the slightest harm or danger from the rapid rise of temperature if the treatment is stopped as soon as the temperature of the colon approaches normal.

VIII. *Alternations of Systemic Temperature.*—Either under light pentobarbital sodium anesthesia or without anesthesia, rats confined in individual wire mesh holders were immersed to the shoulders vertically in ice water. After a selected time they were transferred suddenly to water at 108, 110 or 112 F. (approximately 42, 43 or 44 C.). These alternations were continued under various plans as follows.

Transfers at short intervals of only eight or ten minutes caused comparatively slight effects. The colon temperatures fluctuated only between 89 and 94 F. (31.5 and 34 C.) minimum and 103 and 104 F. (39.5 and 40 C.) maximum. After fifteen changes of this kind, repeated daily for three days, rats were not dangerously exhausted. The feet were bright pink and the tails bluish pink, with moderate edema. They returned to normal within the next two or three days.

Results were the same with alternations between the warm water and room air. Similar alternations between ice water and room air caused frequent fatal chilling.

The largest number of experiments were guided by the animal's condition. Unconsciousness and barely perceptible heart beat indicated the extreme limit of cold tolerance, while urgent struggling and dyspnea were recognizable signs of colon temperatures at the upper safe limits of 105 to 106 F. (40.5 to 41 C.). When light anesthesia is induced, the torpid state mentioned with a colon temperature of about 60 F. (15 C.) may be reached in fifteen to twenty minutes, but without anesthesia struggling may lengthen the time to thirty or forty minutes. The period for attaining the upper temperature in a warm bath may vary from fifteen to thirty minutes according to the water temperature. With fifteen such alternations per day, rats which escaped accidental fatalities died from exhaustion within two or three days. The feet were red and slightly swollen and the tails swollen and cyanotic. The viscera were found grossly normal, except for hyperemia or slight congestion of the lungs. Notwithstanding the edema, blood counts showed absence of hemoconcentration; the condition therefore was not equivalent to burn shock. The entire results were duplicated by similar transitions between the warm water and room air. The governing factors were clearly the degree and duration of heating, while the mere suddenness and extent of temperature change had no appreciable influence.

EXPERIMENTS ON TUMORS

The older literature contained suggestions that heat or fever may conduce to the breakdown of tumors, while Fay more recently demonstrated an inhibiting tendency of cold. Fluctuations of temperature have never been tried. Tumors of the extremities can be subjected to far greater temperature changes than are possible for the entire body. Our special interest arose from previous work[17] which indicated destruction of tumors by an inflammatory reaction, especially that following removal of a tourniquet. It was of interest therefore to learn whether such a reaction might be created or intensified by abnormal temperatures or their fluctuations.

Accordingly, all the preceding types of experiments were repeated with rats bearing the Crocker sarcoma no. 39 implanted in legs, feet or tails. The results of these experiments, totaling hundreds, can be summarized as therapeutically negative. The temporary arrest of tumor growth by any degree or duration of cold had no curative significance. In the preceding work it had been noted that accidental small wounds or ulcers of the extremities became aggravated and extended by prolonged heat or repeated temperature alternations, and, as points of

17. Allen, F. M.: Am. J. Clin. Path. **10**:813-821, 1940; Effects of Local Reactions in Spontaneous Tumors of Animals and Human Beings, Arch. Surg. **41**:79-90 (July) 1940.

impaired resistance, they sometimes led to loss of limbs under conditions in which intact limbs survived. Similarly, the heat treatments could make the poorly nourished central parts of tumors break down and ulcerate, but no temperature or combination of temperatures caused destruction of the vigorous outer parts of tumors selectively as compared with the normal tissues. Even actual freezing, which can destroy some small human tumors, is impracticable in rats because of the inferior resistance of their normal tissues as compared with human tissues. Furthermore, none of the thermal alternations served to sensitize the tumors to the action of tourniquets applied simultaneously or before or afterward.

COMMENT

Rats' tails were mostly used as test objects because of their adaptability to maintaining selected temperatures, and further observations were made on the legs and the larger parts of the body. All deductions from thermal experiments must be guarded with recognition of the wide differences between species, in addition to moisture, pressure, connection with or isolation from the body and other important modifying influences. Under given conditions, however, thermal effect is always the product of temperature and time.

The causation of the "immersion foot" syndrome by continued nonfreezing cold and wetness is familiar, but there has not been cognizance of the more rapid and severe lesion which results from wetness and moderate warmth. The theoretic question of the similar or opposite mechanism of edema under these two conditions remains open.

Our experiments and others in the literature are opposed to recent theories of a critical low temperature below which the tissues are deprived of oxygen by lack of membrane permeability or oxygen dissociation. Notwithstanding the physical and physiologic changes which have been described, for example at 10 C., our experiments show the far better survival of extremities with circulation compared with those without circulation at temperatures below this level, just as hibernating species are known to live for months at these low temperatures though they could not do so without circulation. The outstanding fact is that all departures from the normal level, either downward or upward, are injurious according to the universal law of the product of temperature and time. The smaller the deviation from normal, the longer is the time required for serious or fatal effects. Our examples, in which rather small and prolonged changes produced injuries resembling those of large and brief changes, suggest that still smaller deviations continued still longer may do the same. According to this interpretation, an extremely narrow temperature range is one of the requisites for truly permanent viability of any species of mammal and any of its vital organs.

The therapeutic action of contrast baths is presumably a nervous stimulation, if we judge by animal experiments in which actual tissue temperatures are shifted suddenly between low and high extremes, with no effect other than that obtainable by the heating alone. No more "burn" or other injury is caused by a rapid 70 degree rise from 40 to 110 F. (5 to 43 C.) than by the 10 degree rise from 100 to 110 F. (37.8 to 43 C.).

Without questioning Fay's advice for gradual warming of patients who have become adjusted to several days of hypothermia, there must be emphasis on the necessity of rapid restoration of normal temperature in cases of bodily chilling of ordinary duration. The absence of circulatory failure or other dangers in the animal experiments is confirmatory of clinical observations. Likewise no blistering or other harm results from the rapid warming of chilled local parts to whatever temperature is selected as optimal for therapy. Whether this local temperature should be normal or above or below normal is discussed in an ensuing paper.

The negative effects of rapid fluctuations in temperature on rat tumors are in accord with the principles thus established for normal tissues.

CONCLUSIONS

1. The experiments illustrate the importance of modifying factors, such as moisture and circulation, but under standard conditions thermal effects are the product of temperature and time. Similar destructiveness can result from changes in temperature which are extreme and brief or slight and prolonged.

2. The "immersion foot" type of lesion is produced not only by the familiar combination of nonfreezing cold and wetness but even more rapidly and severely by wetness and moderate warmth.

3. Experiments with ligated limbs add to the known facts which disprove the prevalent fallacy that there is a nonfreezing "critical" temperature below which tissues are unable to utilize oxygen from the blood.

4. Experiments with systemic or local thermal fluctuations show that only absolute temperatures are determining, the mere extent or rapidity of change having no influence. This physiologic law finds two therapeutic applications. Bodily hypothermia of any ordinary duration is best treated by the speediest possible restoration of normal temperature. Likewise no blistering or other harm results from rapid warming of chilled local tissues to an optimum therapeutic temperature.

5. The utmost degree of duration of high or low temperature, locally or systemically, or extreme alternations between temperatures, failed to excite any curative tendency in rat sarcoma or to sensitize it in comparison with the normal tissues.

EXPERIMENTS ON LOCAL HYPOTHERMIA FOR TREATMENT OF BURNS AND FROSTBITE

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THE UNIQUE ability of cold to control simultaneously pain, shock, exudation, bacterial activity, tissue devitalization and toxic absorption has caused it to be recommended [1] for a wide variety of surgical uses, including operative anesthesia and the treatment of burns, frostbite, embolism or thrombosis, crush injuries and other conditions of trauma or infection. Theoretic misconceptions of injury by or tolerance of cold were partly corrected in the preceding paper.[2] Particularly the supposed blocking of oxygen utilization below 10 C. is contradicted by the intense activity of arctic fish [3] as well as the long survivals of hibernating species and of infant mammals [4] at near-freezing temperatures. As a general rule, the injurious effect of any deviation from normal temperature may be measured as a product of temperature and time. The coagulation of protein at upper temperature limits is more immediately and positively fatal than the ice crystal formation at the lower limits. At subfreezing levels there are wide differences of tolerance dependent on factors such as presence or absence of moisture or whether tissues are actually frozen or merely supercooled at the same temperature and whether they are

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1. (*a*) Allen, F. M.: Tr. A. Am. Physicians **52**:189-194, 1937; Am. J. Surg. **41**:192-200, 1938; ibid. **45**:459-464, 1939; Surg., Gynec. & Obst. **67**:746-751, 1938; ibid, **68**:1047-1051, 1939; Surgery **3**:893-898, 1938; Ann. Surg. **108**:1088-1093, 1938; Physical and Toxic Factors in Shock, Arch. Surg. **38**:155-180 (Jan.) 1939; Am. J. Surg. **52**:225, 1941. Crossman, L. W.; Ruggiero, W. F.; Hurley, V., and Allen, F. M.: Reduced Temperatures in Surgery: II. Amputations for Peripheral Vascular Disease, Arch. Surg. **44**:139-156 (Jan.) 1942. (*b*) Allen, F. M.: Refrigeration in General Surgery of Limbs, Am. J. Surg. **68**:170-184, 1945.

2. Safford, F. K., Jr.; Lisa, J. R., and Allen, F. M.: Local and Systemic Effects of Heat and Cold in Rats, Arch. Surg., this issue, p. 499.

3. Field, J., and Peiss, C. N.: Proc. Am. Physiol. Soc. **58**:46-47, 1949.

4. Adolph, E. F.: Am. J. Physiol. **155**:378-387, 1948.

connected with or separated from the body.[5] Likewise, for temperatures somewhat above freezing clinical fallacies have been introduced by disregard of the complicating factors of moisture, position, circulation or even the time limits.[6] The resulting widespread misconceptions are such that refrigeration is not mentioned in a paper on arterial injuries [7] or is declared to damage tissues so that they must be amputated.[8]

Correct regulation of temperature, time and other factors may be assumed as equally necessary in treatments with either heat or cold, but only the latter method has been condemned on the basis of failures due to arbitrary haphazard selections. In the treatment of frostbite, modifying factors may be conceived as accounting for the difference between Greene's [9] favorable results and Davis' [10] unfavorable ones at temperatures lower than those generally approved therapeutically, namely 2 to 5 C. A strong preponderance in favor of hypothermia for both frostbite and immersion foot is created by the clinical reports of Ungley,[11] White,[12] Lesser [13] and Webster, Woolhouse and Johnston,[14] the last authors in particular advocating skin temperatures of the order of 60 to 70 F. (15 to 21 C.).

For lack of space, only the following summary analysis can be offered of conflicting experimental reports, which involve also the questions of slow or rapid rewarming of frozen tissues and pharmacologic treatments.

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5. Webster, J. P.: Ann. Surg. **120**:431-449, 1944. Flatt, A. E.: Lancet **2**:249-251, 1948. Blakemore, A. H.; Lord, J. W., Jr., and Stefko, P. L.: Ann. Surg. **117**:481-497, 1943. Blakemore, A. H., and Lord, J. W., Jr.: Nonsuture Method of Blood Vessel Anastomosis: Experimental and Clinical Study, J. A. M. A. **127**:685-691 (March 24) and 748-753 (March 31) 1945. Allen, F. M.: Canad. Med. A. J. **51**:220-226, 1944; Clinics **4**:1642-1674, 1946. Safford and others.[2]

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12. White, J. C.: New England J. Med. **228**:211-222 and 241-247, 1943.

13. Lesser, A.: Ann. Surg. **121**:257-271, 1945.

14. Webster, D. R.; Woolhouse, F. M., and Johnston, J. L.: J. Bone & Joint Surg. **24**:785-794, 1942.

(*a*) Investigations have often been colored by preconceived theories of membrane permeability and oxyhemoglobin dissociation. (*b*) The arbitrarily selected therapeutic temperatures have been generally too low or too long continued. (*c*) Cooling has often been employed in such a manner as to delay thawing of frozen tissues, so that the actual duration of freezing has been unequal in treated and control animals. (*d*) Because of species differences in tolerance to both temperature and time, results in rodents are often not valid for application to man. The following conclusions can be drawn for the treatment of frostbite. 1. Regarding hypothermic treatment, the adverse reports of Lange,[15] Quintanilla, Krusen and Essex [16] and Lempke and Shumacker [17] are eliminated on one or more of these grounds, leaving the favorable findings of Fuhrman and Crismon [18] in harmony with clinical experience. 2. Rapid rewarming of frozen parts is convincingly upheld by Fuhrman and Crismon [19] and Lempke and Shumacker, against the earlier uncertainty of Harkins and Harmon.[20] 3. The benefit of prevention of thrombosis by heparin, as demonstrated in human subjects by Lange and his co-workers, is not overthrown by the negative experiments on rabbits of Quintanilla, Krusen and Essex or of Fuhrman and Crismon.[21] 4. Sufficiently severe or prolonged freezing may cause necrosis from vascular damage in spite of prevention of thrombosis by heparin or dicumarol,® and the introduction of rutin [21] to protect vessel walls or reduce permeability marks an important further advance. Reduced temperature is known to retard clotting and also preserve vitality of tissues and blood vessels. The foregoing analysis thus harmonizes the conflicting reports in the literature and also the relation of hypothermia to other treatments.

For burns, the principle of controlling pain, shock, infection and tissue devitalization is upheld by clinical experience with hypothermic

15. Lange, K., and Boyd, L. J.: Science **102**:151-152, 1945; Surg., Gynec. & Obst. **80**:346-350, 1945. Lange, K., and Loewe, L.: ibid. **82**:256-260, 1946. Lange, K.; Weiner, D., and Boyd, L. J.: New England J. Med. **237**:383-389, 1947.

16. Quintanilla, R.; Krusen, F. H., and Essex, H. E.: Am. J. Physiol. **149**: 149-161, 1947.

17. Lempke, R. E., and Shumacker, H. B.: Studies in Experimental Frostbite, Yale J. Biol. & Med. **21**:321-334, 1949.

18. Crismon, J. M., and Fuhrman, F. A.: The Use of Casts and Pressure Dressings in the Treatment of Severe Frostbite, J. Clin. Investigation **26**:486-496, 1947.

19. Fuhrman, F. A., and Crismon, J. M.: Treatment of Cold Injury by Means of Immediate Rapid Warming, J. Clin. Investigation **26**:476-485, 1947.

20. Harkins, H. M., and Harmon, P. H.: Thermal Injuries: Effects of Freezing, J. Clin. Investigation **16**:213-221, 1937.

21. Fuhrman, F. A., and Crismon, J. M.: The Effect of Rutin and Other Chemical Agents on the Course of Experimental Frostbite in Rabbits, J. Clin. Investigation **27**:364-371, 1948.

treatment, either locally [22] or with cool baths [23] or cold air [24] for extensive surfaces. Comfort can be maintained without opiates, dressings are changed painlessly, débridement, special cleansing and elaborate asepsis are obviated, fever and intoxication are controlled and more tissue is saved than by any other method. Experimentally, it is desirable to explain the discrepancy between these clinical observations and the poor results obtained by Baxter and More [25] in the treatment of scalded tails of rats with dry air at temperatures from 40 to 60 F. (5 to 15 C.).

EXPERIMENTAL METHODS

Rats, confined in individual holders as previously described,[2] were briefly and deeply etherized while the tail or other selected parts of the body were dipped in water at 90 C. Legs and body were shaved before scalding. During the treatments of ears, body or tails the animals were asleep under pentobarbital sodium anesthesia, moderately sedated or awake respectively. No perceptible differences were introduced by beginning hypothermia immediately or at intervals of two or more minutes after scalding. The factor of immobilization was tested by keeping some rats in roomy cages in a large refrigeration vault for ten to fourteen days after scalding, with results no different than those reported by Baxter and More for their confined rats. The time limits for the main mass of experiments were fixed by three considerations, namely, the necessity of avoiding "immersion foot" lesions with the wet cold, the benefit of even brief immediate chilling of burns in human patients and the inferior thermal tolerance of rats as well as the far greater magnitude of the same absolute time period relative to their high metabolism and short life. Therefore the treatments were measured in hours rather than days.

HYPOTHERMIC TREATMENT OF SCALDS

Table 1 shows illustrative experiments, which are typical of larger numbers with only infrequent exceptions. The ears were chosen as thin enough for almost immediate temperature change in all tissues and blood vessels. In the experiments with larger areas, the greatest damage naturally occurred in the parts which were most thoroughly penetrated

22. (*a*) Allen, F. M.; Crossman, L. W., and Safford, F. K., Jr.: New York State J. Med. **43**:951-952, 1943. (*b*) Rose, H. W.: Northwest Med. **35**:267-270, 1936. (*c*) Kross, I.: Low Temperature Therapy for Preservation of Limbs, J. A. M. A. **128**:19-20 (May 5) 1945. (*d*) Safford, F. K., Jr., and Nathanson, M. B.: Clinical Observations on Tissue Temperatures: Pathologic and Therapeutic Effects, Arch. Surg. **49**:12-22 (July) 1944. (*e*) Allen.[1b]

23. Leonardo, R. A.: J. Internat. Coll. Surgeons **10**:79-91, 1947.

24. Brown, H. R., and de Lalla, V.: Arch. Phys. Med. **30**:98-102, 1949.

25. Baxter, H., and More, R. H.: Ann. Surg. **125**:177-193, 1947.

by heat and which incidentally were supplied by end arteries, namely, the toes and tails. In general, the benefits of hypothermia are clearly

TABLE 1.—*Hypothermic Treatment After Scalding*

Rat No.	Part of Body Scalded	Time at 90 C. (Seconds)	Treatment	Result
1	Ear	1	Control, untreated	Ear mummified and lost
2	Ear	1	Ear in imperfect contact with block of ice for 1¼ hr.	Inflamed and vesicated, but only margin lost
3	Ear	1	Ear in ice water for 1¼ hr.	Result the same as in no. 2
4	Tail	4	Control, in air at 70 F.	Early cyanosis, increasing to necrosis and mummification of entire tail
5	Tail	4	Water at 100 F. for 1 hr.	Accelerated cyanosis and necrosis
6	Tail	4	Ice water 7 hr.	Cyanosis; final necrosis of 5 cm. at end of tail
7	Tail	4	Water at 70 F. for 7 hr.	Less cyanosis; final loss of 3 cm. at tail tip
8	Tail	4	Ice water 1 hr., then water at 70 F. for 6 hr.	Slight pinkish cyanosis; final necrosis of 1 cm. at tail tip
9	Hindquarters to waist	1	Control, untreated in air at 70 F.	Severe vesication; final loss of toes and most of tail
10	Hindquarters to waist	1	15 min. in ice water	Moderate vesication; only tips of toes finally lost
11	Hindquarters to waist	2	Control, untreated in air at 70 F.	Inflammation and vesication, especially of toes; death in 8 days, with dark crusts of skin, mummification of feet, necrosis of tail
12	Hindquarters to waist	2	20 min. in water at 65 F.	Vesication slight on body, severe on feet and tail; ulceration and infection; death in 14 days
13	Hindquarters to waist	2	20 min. in ice water	Vesication limited to feet and tail; survived, with loss of some toes and 5 cm. of tail
14	Hindquarters to waist	10	Control, untreated in air at 70 F.	Skin necrosis; death in 4 days
15	Hindquarters to waist	10	20 min. in ice water, reducing rectal temperature to 70 F.	Skin necrosis; death in 7 days
16	Body vertically to shoulders	1	Control, untreated in air at 70 F.	Ecchymoses of skin; vesication of feet; skin of tail swollen; died in 3 days
17	Body vertically to shoulders	1	4 min. in ice water	Skin lesions apparently greater than in control; died in 3 days
18	Body vertically to shoulders	1	8 min. in ice water	Somewhat less ecchymosis; much less vesication of feet; died in 3 days
19	Body vertically to shoulders	2	Control, untreated in air at 70 F.	Died in 5 days, with feet and tail necrotic, extensive vesication of body
20	Body vertically to shoulders	2	2 hr. in water at 60 F.	Died in 4 days, with feet and tail necrotic, body slightly less vesicated than control
21	Body vertically to shoulders	2	20 min. in ice water, reducing rectal temperature to 56 F.; apparently dead; revived in water at 100 F. for 30 min. raising rectal temperature to 78 F.; after warm dry wrapping for 1 hr., active with rectal temperature 92 F.; left at room temperature of 68 F.	Vesication of feet and tail, very little of body; for 1 week seemed recovering, with loss of all toes and 3 cm. of tail; died on 8th day

evident in cases of diminished tissue injury or lengthened survival. Ice water may have been superior for the shortest treatments and milder cooling for longer treatments. Similar experiments with scalding of the tips of ears and tails of cats and dogs were too few for definite reporting

but sufficient to show confirmatory benefits. No attempt was made to establish the optimum time or temperature for any species, as the figures would not necessarily hold good for man, and the short treatments which are preferable for rats certainly do not imply any similar brevity of clinical hypothermia. The one result arrived at was the definite and positive benefit of hypothermia in the treatment of burns.

HYPOTHERMIC TREATMENT OF FROSTBITE

The lesions of burning and freezing are frequently classed as similar, but an important difference lies in the greater destructiveness of heat, inasmuch as tissues which are severely burned through and through are hopeless, while those which are solidly frozen through and through are treated, with or without success. In the extremities the freezing of end arteries may create greater danger of necrosis than equal freezing of areas of the body or face, which can receive collateral circulation. Experiments must be conducted with appreciation of the differences between animal species. In connection with burns, the differences in thermal reactions were mentioned in explanation of the brevity of hypothermic treatment in the rat as compared with man. Other known differences in the response to cold are the following: (*a*) As mentioned in the preceding paper,[22c, d] the rat's tolerance for bodily hypothermia is much greater in degree (down to about 13 C., or 56 F.) but much less in time (death in a day or less from a temperature which a man may endure for a week). (*b*) Brain and liver tissue and large blood vessels of the dog and of man can be frozen for one minute with carbon dioxide ice and recover without microscopically discoverable damage,[26] but similar freezing of these structures or slightly longer freezing of the limbs of rats furnishes examples of irreparable necrosis beyond the aid of heparin or other known treatment. (*c*) In the rat, reduced temperature protects against shock of peripheral origin, for example, that produced by tourniquets or wounds of the legs, but it aggravates shock of splanchnic origin, e. g., intestinal trauma or stasis.[27] In the dog and cat, the reduced temperature protects against shock of either origin, and this result, not the exceptional result in the rat, is presumably applicable clinically.

It was therefore necessary to regulate experimental freezing according to the animal species and the part of the body. Simple pressure between two pieces of carbon dioxide ice was found to give satisfactory uniformity of results, when a single operator kept the pressure and other details uniform. For rats' tails the procedure was varied by thus freez-

26. Ebin, J.: Surg., Gynec. & Obst. **76**:43-50 and 456-459, 1943; Solid Carbon Dioxide-Ferric Chloride Technic for Hemostasis: Experimental Study of Its Effectiveness in Brain Viscera and Superior Saggital Sinus, Arch. Surg. **46**:386-394 (April) 1943.

27. Allen, F. M.: J. Internat. Coll. Surgeons **11**:278-281, 1948.

ing a segment about 1 cm. wide located 3 to 4 cm. from the tail tip. Judgment could then be based on the depth of the annular ulcer in the frozen zone and also the viability of the part distal to it. The lesions from one or two minutes of such freezing were suitable for therapeutic tests, but with three minutes no kind of thermal treatment could prevent total necrosis. Since the critical time for tails and also for feet was so short, and the still shorter time for ears was measured in seconds, an important source of error appeared when it was found that immediate immersion in ice water could lengthen the duration of the frozen state by one to several minutes. This was sufficient to spoil any possible benefits of refrigeration in the rodents, and real comparisons could be made only when the treated and control tails were equally thawed for a few minutes before treatment was begun. With the longer freezing time tolerated by dogs and cats this increment of freezing was relatively less important, though not negligible, and the benefit of refrigeration might be sufficient to be demonstrable in spite of this inequality.

Rats' ears were frozen by pressure between pieces of carbon dioxide ice for thirty or forty-five seconds. The violent inflammation followed by necrosis was not prevented by immediate immersion in ice water. Thawing for a few seconds in water at 100 F. and subsequent immersion in ice water or especially water at 60 to 70 F. (15 to 21 C.) for two or three hours sometimes saved the basal part of the ear but not with regularity enough to be dependable. This plan was given up as unsatisfactory.

The tails of 76 rats had segments frozen in the manner described previously for one or two minutes. Various details were changed in all the series. Controls were either left untreated or received preliminary thawing like the treated animals. In either case they were then left exposed to air which on different days varied from 70 to 92 F. (21 to 33 C.), without any positive difference in results. The treated tails were immersed in water at 40, 60, 80 or 100 F. (5, 15, 22, 38 C.) for periods of one to six hours, either immediately after freezing, after thawing in water at 100 F. (38 C.) for one to five minutes or after being exposed to room air for five to fifteen minutes before treatment. The criteria for judgment were the depth of ulceration, the time required for healing and the viability of the terminal segment of the tail.

As is evident from the number of variables in this group of rats, the tests were exploratory and could not furnish statistics. The harmfulness of immediate cooling which prolonged the frozen state was uniform and decisive. The most favorable duration of treatment lay probably between the extremes of one and six hours. Ice water appeared inferior to moderate cooling between 60 and 70 F. (15 to 21 C.), and there was no distinct advantage in beginning with ice water and raising the temperature gradually. Notwithstanding a general impression of benefit from

cooling, the differences were slight and subject to unexpected exceptions. It appeared that rats and perhaps other rodents, owing to their peculiar thermal reactions, are unsatisfactory for tests having clinical application.

With regard to cats and dogs, evident resemblances to man are found in the tolerated time of freezing and the response to thermal therapy.

TABLE 2.—*Hypothermia After Freezing in Cats*

No. of Cats	Part Frozen	Time, Minutes	Treatment	Result
2	Ear	2	3 hr. in ice water	Severe vesication; 1 lost, 1 healed with epilation
1	Ear	2	Thawed 1 min. at 104 F., then 3 hr. in ice water	Vesication; normal healing
2	Ear	2	3 or 5 hr. in water at 60 F.	Vesication; normal healing
2	Ear	2	Controls, untreated	Necrosis and loss of ear
2	Tail tip	5	Controls, untreated	Necrosis
1	Tail tip	5	5 hr. in water at 100 F.	Accelerated necrosis
1	Tail tip	5	5 hr. in ice water	Healed; hair growth doubtful
1	Tail tip	5	Thawed 2 min. at 105 F., then 2 hr. in ice water, followed by 3 hr. at 60 F.	Healed normally
1	Tail tip	5	5 hr. in water at 60 F.	Healed normally

TABLE 3.—*Hypothermia After Freezing in Dogs*

No. of Dogs	Part Frozen	Time, Minutes	Treatment	Result
2	Ear tip	6	Controls; 1 untreated, 1 thawed 2 min. in water at 108 F.	Necrosis
1	Ear tip	6	6 hr. in ice water	Intense vesication; healed, with partial deformity of frozen part
1	Ear tip	6	Thawed 2 min. at 108 F., then 6 hr. in ice water	Vesication; healed normally
1	Ear tip	6	6 hr. in water at 60 F.	Vesication; healed normally
1	Ear tip	6	1 hr. in ice water; then 5 hr. in water at 60 F.	Vesication; healed normally
2	Tail tip	6	Controls; 1 untreated, 1 thawed 2 min. in water at 108 F.	Necrosis
1	Tail tip	6	8 hr. in water at 102 F.	Accelerated necrosis
1	Tail tip	6	8 hr. in ice water	Necrosis of skin; deep tissues remained red and inflamed 3 wk., then mummified
1	Tail tip	6	8 hr. in water at 60 F.	Healed normally
1	Tail tip	6	Thawed 2 min. in water at 108 F., then 2 hr. in ice water and 6 hr. in water at 60 F.	Healed normally
3	2 skin patches each	6	One patch on each dog untreated as control; ice bag on the other for 6 hr.	In 2 dogs, treated area formed much smaller ulcer and healed more rapidly; in the third dog, opposite result may have been due to misplaced ice bag

Fewer animals could suffice because the results were consistent, as shown in tables 2 and 3. Though the benefit of hypothermia generally outweighed the delay of thawing by ice water, preliminary thawing distinctly improved the results, and a temperature higher than 108 F. (42 C.) could doubtless have been used to advantage, especially if the mass of frozen tissue had been larger. While the milder cooling at 60 F. (15 C.) appeared generally more beneficial than ice water at 40 F. (5

C.), no attempt was made to decide the optimum temperature or time or the possible advantage of beginning with ice water and raising it gradually to the higher temperature.

COMMENT

The observations agree with the interpretation of the literature at the beginning of this paper. As mentioned, the experiments aimed only to establish the general principle of harmfulness of high temperature and benefit of low temperature and not the optimum degree or duration of hypothermia for any species, especially as such data for animals are not transferable to man without direct proof. Existing clinical experience has suggested the need of much longer duration of hypothermia in human patients and also of moderation in the degree of cooling as a rule, with exceptions when brief radical refrigeration is required for emergencies such as burn shock or acute intoxication. Results will vary according to experience and skill, just as with other forms of treatment.

The harmfulness of prolonging the frozen state should be contrasted with the harmlessness of sudden wide changes of temperature. These facts have not been correctly appreciated in either folk medicine or scientific surgery. There is neither risk nor inconsistency in using a high temperature for brief thawing and quickly replacing it with a low temperature for sustained treatment. Clinical results should be improved by this innovation. Also it is reasonable to regard thermal and pharmacologic treatment as supplementary and not antagonistic.

SUMMARY AND CONCLUSIONS

1. For treatment of burns, hypothermia in the form of several hours' immersion in water at reduced temperatures was found beneficial in rats.

2. For treatment of frostbite, rats (and perhaps other rodents) appear unsuited for testing hypothermic therapy.

3. In cats and dogs even brief prolongation of the frozen state increases injury. Beneficial effects were observed when the frozen tissues were treated by rapid thawing followed by moderate cooling.

PSEUDOCYSTS OF THE PANCREAS; TOTAL EXCISION

Report of a Case

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PANCREATIC cysts are still encountered so infrequently in the clinical experience of any one surgeon that the question of their proper treatment is still of interest. According to Berkay,[1] pseudocysts of the pancreas constitute 40 per cent of all pancreatic cysts. Table 1 summarizes the experience of thirty-five contributors in the past, between the years 1861 and 1949, in which 306 proved pseudocysts of the pancreas were encountered and 40 of these, or 13.07 per cent, were completely excised. On the basis of these facts, the available literature has been summarized, the records of 209,813 consecutive patients admitted at the Hollywood Presbyterian Hospital in the past twenty-five years studied and the following case report submitted.

HISTORY

Claessen [2] in 1842 reviewed the literature and made a collection of individual case reports of pancreatic cysts. Friedreich [3] in 1878 stated: "The treatment [of cysts of the pancreas] must be of the symptoms as they arise and by diet." Körte [4] in 1898 reported on 121 instances of pancreatic cysts from the literature, 60 of which involved males. Guleke [5] completely reviewed the surgical literature between the years 1882 and 1911 and listed some 260 instances of pancreatic cysts operated on. Heinrich Muller [6] cited the literature on pancreatic cysts and was able to add 166 further examples between the years 1912 and

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1. Berkay, F. M.: Pseudocysts of the Pancreas and External Drainage, J. Internat. Coll. Surgeons **11**:403-420 (July-Aug.) 1948.

2. Claessen, H. J.: Die Krankheiten der Bauchspeicheldrüse, Cologne, M. Du Mont-Schauberg, 1842, p. 368.

3. Friedreich, N.: Cysts of the Pancreas, in von Ziemssen, H.: Cyclopedia of the Practice of Medicine, New York, William Wood & Company, 1878, vol. 8, p. 615.

4. Körte, W.: Die chirurgischen Krankheiten und die Verletzungen des Pankreas, in von Bergmann and von Bandl: Deutsche Chirurgie, Stuttgart, F. Enke, 1898, vol. 45, p. 234.

5. Cited by Berkay.[1]

6. Cited by Berkay.[1]

1929. Berkay [1] estimated in 1948 that the number of cases of traumatic pseudocysts recorded in the surgical literature was then probably in the neighborhood of 215.

CLASSIFICATION

According to Oser [7] and McWhorter,[8] pseudocysts of the pancreas are cysts resulting from hemorrhage, degeneration and necrosis. These

TABLE 1.—*Reported Instances of Total Excision of Pseudocysts of the Pancreas*

Author	Year	Total No. of Cysts of All Types	Pseudocysts	
			Total No.	No. Excised
Bozeman [39]	1861	1	1	1
Lloyd [17]	1892	2	2	0
Mayo, W. J. [33]	1894	1	1	0
Railton [18]	1896	1	1	0
Oser [7]	1903	..	134	11
Tellig and Dobson [19]	1909	1	1	0
Willis [40]	1915	1	1	1
Kerr [20]	1918	2	2	0
Russ [21]	1921	1	1	0
Primrose [23]	1922	1	1	0
Bouman [42]	1922	1	1	1
Ehla [20]	1923	1	1	1
Bernard, Dumet and Cotte [44]	1924	1	1	1
Saugues: Cited by Lahey and Lium [46]	1925	1	1	1
McWhorter [8]	1925	..	14	1
Villaret, M., and Justin-Besancon, L.: Arch. d. mal. de l'app. digestif. **15**: 751 (Oct.) 1925	1925	1	1	1
Judd, Mattson and Mahorner [14]	1931	81	47	7
Koucky, J. D., Beck, W. C., and Todd, M. C.: Surg., Gynec. and Obst. **73**: 113 (July) 1941	1941	6	6	0
Rabinoviteh and Pines [13]	1942	17	11	3
Harrison and Cooper [43]	1943	1	1	1
Pinkham [16]	1945	10	10	0
Adams and Nishijima [24]	1946	9	6	2
Acuff [47]	1947	12	2	0
Shallow, Eger and Wagner [12]	1947	..	4	0
Cooper, F.: Personal communication to the author	1947	..	1	1
Carter, R. F., and Slattery, L. R.: Surg. Clin. North America **27**: 411 (April) 1948	1948	6	3	2
Warren [38]	1948	7	2	0
Bickford [51]	1948	2	2	0
Berkay [1]	1948	..	5	0
Mousseau and Kling [45]	1948	1	1	0
Meyer, Sheridan and Murphy [15]	1949	31	31	2
Anglem and Lee [37]	1949	..	2	0
Poer and Stephenson [26]	1949	3	3	0
Schiffbauer, H. E.: Personal communication to the author	1949	..	2	2
Collins, D. C.	1949	9	3	1
Totals 35 Contributions	1861-1949	211	306	40
Per cent of pseudocysts of the pancreas excised completely				13.07

are further subdivided into (*a*) intrapancreatic causes, such as degeneration of tumors arising from sarcomas or carcinomas, trauma, vascular diseases and pancreatitis and (*b*) extrapancreatic causes which originate from the same factors as those just listed. Körte [9] believed that pseudo-

7. Oser, L.: Diseases of the Pancreas, in Nothnagel, H.: Encyclopedia of Practical Medicine, Philadelphia, W. B. Saunders Company, 1903, p. 180.

8. McWhorter, G. Lewis: Cysts of Pancreas, Arch. Surg. **11**:619-632 (Oct.) 1925.

9. Körte, W.: Zur Behandlung der Pankreascysten und Pseudocysten, Deutsche med. Wchnschr. **37**:536-538 (March 23) 1911.

cysts or cystoids constitute one of the two major types of pancreatic cysts, the second type being true glandular cysts of the pancreas itself. Berkay [1] stated that pseudocysts are those in which an accumulation of fluid occurs, which is produced as the result of trauma, pancreatic necrosis or degenerative changes occurring in the interstitial tissue of the pancreas. Pseudocysts, according to Berkay,[1] may be further divided into two fundamentally different types. The first, degeneration cysts, are usually the end result of an acute pancreatic necrosis, characterized by the liquefaction of dead pancreatic tissue or caused by the autodigestion of effused blood. According to Lazarus,[10] they may likewise result from toxic or infected lesions which occur in general sepsis as well as in typhoid and from the degeneration of tissue caused by cancer or sarcoma. The second major group is the post-traumatic or postpancreatic cystoids. Körte [11] believed that the largest number of pancreatic cysts coming to operation belonged to this subtype. This type of cyst was differentiated from the true glandular or degenerative

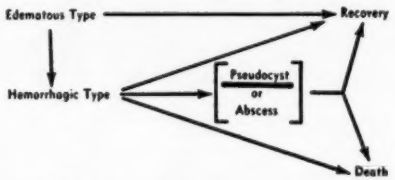

Fig. 1.—Clinical course of acute pancreatitis. Diagram illustrating one of the two chief methods whereby pseudocysts of the pancreas are caused. (From Shallow, Eger and Wagner.[12])

cysts by its anatomic position, which was usually outside of the substance of the pancreas and generally appeared in the lesser omental sac. This variety of cyst possesses neither a proper wall nor an epithelial lining. The wall is composed of the peritoneal boundaries of the lesser omental sac and the walls of adjacent organs. The cystic contents comprise in part a more or less heterogeneous and liquefied necrotic self-digested pancreatic tissue, composed partially of inflammatory exudate and usually a considerable amount of altered blood. Figure 1, taken from Shallow, Eger and Wagner,[12] graphically illustrates the usual causation of a pancreatic pseudocyst. Most authors agree that there is nearly an

10. Lazarus, P.: Beitrag zur Pathologie und Therapie der Pankreaserkrankungen mit besonderer Berücksichtigung der Cysten und Steine, Ztschr. f. klin. Med. **51**:203-210, 1904.

11. Cited by Berkay.[1]

12. Shallow, T. A.; Eger, S. A., and Wagner, F. B., Jr.: Acute Pancreatitis: Medical and Surgical Management, Postgrad. Med. **2**:288-301 (Oct.) 1947.

equal distribution of pseudocysts of the pancreas between the male and female sex. Rabinovitch and Pines,[13] however, report that all their 11 tumors occurred in females.

ETIOLOGIC FACTORS

Körte[9] recorded a history of trauma in 28 per cent of 117 instances. Judd, Mattson and Mahorner[14] elicited a history of trauma in only 1 of 45 instances of pancreatic pseudocysts. Meyer, Sheridan and Murphy[15] listed an incidence of trauma of 51.6 per cent in 31 cases. Pinkham[16] stated that in his series of 10 patients with pancreatic pseudocysts 20 per cent gave a preceding history of trauma. Lazarus[10] reported that 30 per cent of his patients had previous trauma. According to Lloyd,[17] a blow to the upper portion of the abdomen, particularly to the epigastrium, may crush the pancreas against the bodies of the first and second lumbar vertebrae, thereby tearing its thin serosal capsular covering. Bleeding follows, resulting in a hematocele, usually forming in the lesser omental sac. On the other hand, a considerable portion of pseudocysts of the pancreas have been frequently associated with a preceding acute hemorrhagic pancreatitis, followed by acute or subacute pancreatic necrosis. Under these conditions the autodigestive role of the activated trypsin and the enzymatic activity of the lipase of the pancreatic juice, resulting from injury and tearing of the pancreatic acini, lobules and secretory ducts, set up an inflammatory collection of pancreatic fluid, which encysts itself in the lesser omental sac.

Traumatic pseudocysts of the pancreas are not solely confined to the adult. Railton[18] reported a pseudocyst of the pancreas occurring in a 6 month old infant. Two paracenteses were done successfully, but the patient failed to survive marsupialization and drainage of the large pseudocyst and died of shock on the fourth postoperative day. Telling and Dobson[19] in 1909 added an additional instance in an 11

13. Rabinovitch, J., and Pines, B.: Cysts of the Pancreas, Arch. Surg. **45**:727-746 (Nov.) 1942.

14. Judd, E. S.; Mattson, H., and Mahorner, H. R.: Pancreatic Cysts: Report of 47 Cases, Arch. Surg. **22**:838-849 (May) 1931.

15. Meyer, K. A.; Sheridan, A. I., and Murphy, R. F.: Pseudocysts of the Pancreas: Report of 31 Cases, Surg., Gynec. & Obst. **88**:219-229 (Feb.) 1949.

16. Pinkham, R. D.: Pancreatic Collections (Pseudocysts) Following Pancreatitis and Pancreatic Necrosis, Surg., Gynec. & Obst. **80**:225-235 (March) 1945.

17. Lloyd, J.: Injury to the Pancreas: A Cause of Effusion into the Lesser Peritoneal Cavity, Brit. M. J. **2**:1051-1054 (Nov. 12) 1892.

18. Railton, T. C.: A Case of Pancreatic Cyst in an Infant, Brit. M. J. **2**:1318-1319 (Oct. 31) 1896.

19. Cited by Rabinovitch and Pines.[13]

month old child. Ehla [20] cited a true pseudocyst of the pancreas in a 5 month old girl. This was totally excised. The specimen measured 6.5 by 18 cm. and weighed 99 Gm. This child made an excellent recovery.

Mayo [21] in 1894 marsupialized a large pancreatic cyst which developed during the course of a pregnancy, and his patient made an uneventful convalescence. Russ [22] recorded a pseudocyst of the pancreas following an acute hemorrhagic necrosis of the pancreas, which developed concurrently with sepsis following childbirth in a 21 year old woman. This pseudocyst had caused a partial obstruction of the small intestine. The cyst was marsupialized, and the patient made an excellent recovery. Primrose [23] listed a similar instance of a pseudocyst of the pancreas developing immediately after childbirth, which burrowed behind the posterior parietal peritoneum. This cyst was totally extirpated by an extraperitoneal approach.

According to Takayasu,[24] who reviewed 131 instances of pancreatic cysts, 30 patients gave a traumatic history and in 15 of these the cyst developed within three months after the trauma. Lloyd [17] in 1892 stated that most pseudocysts of the pancreas developed after abdominal injury and were not true retention cysts. He recorded 2 examples, diagnosed three weeks and three months respectively after trauma. He was the first to call attention to the fact that pseudocysts of the pancreas are really effusions into the bursa omentalis. Johnson and Lee [25] described 5 patients with cysts of the pancreas. One had a malignant cyst which caused death. Three pseudocysts were drained. One cyst was totally excised, but it proved to be a true retention cyst. Kerr [26] listed 2 pseudocysts of the pancreas, both being primarily marsupialized and drained. In the first case the cyst was completely excised at a secondary operation. McWhorter,[8] reporting on 14 pseudocysts of the pancreas, mentioned 1 patient, a woman aged 35, who underwent

20. Ehla, C. E.: Case of Congenital Pancreatic Cyst, J. A. M. A. **78**:1294-1295 (April 29) 1923.

21. Mayo, W. J.: Pancreatic Cyst, Med. Rec. **45**:168 (Feb. 10) 1894.

22. Russ, W. B.: Pseudocyst of Pancreas Apparently Due to Hemorrhagic Necrosis Occurring During the Course of General Sepsis, J. A. M. A. **77**:620-621 (Aug. 20) 1921.

23. Primrose, A.: Pancreatic Cysts and Pseudocysts: Report of a Case of Total Extirpation by an Extraperitoneal Method, Surg., Gynec. & Obst. **34**:431-436 (April) 1922.

24. Takayasu, M.: Beitrag zur Chirurgie des Pancreas, Mitt. a. d. Grenzgeb. Med. u. Chir. **3**:89-96, 1898.

25. Johnson, T. A., and Lee, W. E.: Pancreatic Cyst: Report of 5 Cases, S. Clin. North America **22**:1677-1692, 1942.

26. Kerr, A. A.: Cysts and Pseudocysts of Pancreas, with Report of Cases, Surg., Gynec. & Obst. **27**:40-44 (July) 1918.

excision of the pseudocyst and suffered from a persistent draining sinus for many months thereafter. This patient was originally described by H. Richter.

Anglem and Lee [27] recorded the histories of 20 patients suffering from acute pancreatitis. In 2 of these patients pseudocysts subsequently developed. One was a woman aged 35 whose cyst was marsupialized, and she recovered. The second instance was of a man aged 37 whose pseudocyst was drained. Three and a half weeks postoperatively pancreatic enzymes from the site of origin of the pseudocyst eroded into a large blood vessel, causing a fatal hemorrhage.

Le Dentu [28] is said to have been the first to suggest that a pancreatic cyst might result from hemorrhage arising from the pancreatic tissue after trauma. Bonneau [29] mentioned that pseudocysts more commonly occur after hemorrhagic pancreatitis than after trauma. An excellent recent review on diseases of the pancreas and the subsequent formation of pseudocysts was presented this year by Elman and Lemmer.[30] The contribution made by Archibald in 1919 [31] was of major importance. He showed that pancreatitis could be experimentally produced in animals by increasing the resistance of the sphincter of Oddi of the common bile duct at its juncture with the duodenum.

CLINICAL INCIDENCE OF PANCREATIC CYSTS

White [32] in 1897, reporting from Guy's Hospital in London, encountered 3 instances of pancreatic cyst in 6,078 consecutive autopsies. Judd, Mattson and Mahorner [14] in 1931 stated that in 723,397 consecutive patients admitted to the Mayo Clinic at Rochester, Minn., 81 pancreatic cysts had been treated surgically, 7 of which were completely excised, the largest measuring 20 cm. in diameter. Angel [33] mentioned that between the years 1930 and 1938, 3,600 consecutive abdominal sections had been performed in his hospital and a pancreatic cyst was

27. Anglem, T. J., and Lee, W. F.: Acute Pancreatitis and Its Sequelae, Arch. Surg. **58**:484-488 (April) 1949.

28. le Dentu, M.: Rapport sur l'observation précédente. Bull. Soc. anat. de Paris **10**:197-198 (March) 1865.

29. Bonneau, R.: Pseudo-kystes traumatiques, Presse méd. **30**:701-702 (Aug. 16) 1922.

30. Elman, R. and Lemmer, R. A.: The Pancreas: Contributions of Clinical Interest Made in 1947, Gastroenterology **12**:375-390 (March) 1949.

31. Archibald, E.: The Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common Duct Sphincter, Surg., Gynec. & Obst. **28**:529-545 (June) 1919.

32. White, H.: Diseases of the Pancreas, Guy's Hosp. Rep. **54**:17-63, 1897.

33. Angel, E.: Pancreatic Cysts, South. Med. & Surg. **100**:57-61 (Feb.) 1938.

encountered only once in that series. Adams and Nishijima,[34] writing from the Lahey Clinic, remarked that between the years 1926 and 1945 only 9 instances of pancreatic cysts were encountered. Six of these were true pseudocysts, and 2 were completely excised. Berkay [1] stated that in 14,000 patients admitted to the First Surgical Clinic of the Istanbul University Faculty of Medicine between 1938 and 1946 there were only 5 recorded examples of pseudocysts of the pancreas. Kenneth Warren [35] in 1948 summarized that up to that time only 16 instances of pancreatic cysts had been encountered in the Lahey Clinic. Meyer, Sheridan and Murphy [15] in 1949 said, after a study of the records of the departments of surgery at the Northwestern University Medical School and the Cook County Hospital, that 31 true pseudocysts of the pancreas were found. Poer and Stephenson [36] in 1949, writing from the Whitehead Department of Surgery, Emory University, and the Grady Memorial Hospital, Atlanta, Ga., described 3 cysts of the pancreas.

A search of the records at the Hollywood Presbyterian Hospital, Hollywood, Calif., between the years 1924 and July 1, 1949, revealed 9 cysts of the pancreas occurring in 209,813 patients admitted consecutively, or an incidence of 0.004 per cent. There were 3 proved pseudocysts of the pancreas in these 9 instances, or 33.3 per cent of all the cysts. These 3 pseudocysts represented an incidence of 0.001 per cent of the total patients admitted for this twenty-five year period. Stated another way, one true pseudocyst of the pancreas occurred for every 69,666 consecutive patients admitted to the hospital. Only 1 pseudocyst of the 3 was totally excised. One patient of 6 operated on for various types of pancreatic cysts died (case 8), a mortality percentage of 16.6. The 3 patients with pseudocyst of the pancreas operated on lived.

Table 2 summarizes the data mentioned.

DIAGNOSIS

The diagnosis of a pseudocyst of the pancreas can only be made postoperatively by the pathologist. Preoperatively the surgeon can merely state that the patient has a cyst of the pancreas. A preceding history of trauma or of acute hemorrhagic pancreatitis may lend support to a presumptive preoperative diagnosis of a traumatic or hemorrhagic

34. Adams, R., and Nishijima, R. A.: Surgical Treatment of Pancreatic Cysts, Surg., Gynec. & Obst. **83**:181-187 (Aug.) 1946.

35. Warren, K. W.: Pancreatic Cysts, S. Clin. North America **28**:753-760 (June) 1948.

36. Poer, D. H., and Stephenson, R. H.: Late Results in Treatment of Pancreatic Cysts by Internal Drainage, Surg., Gynec. & Obst. **89**:257-263 (Sept.) 1949.

TABLE 2.—*Instances of Cysts of Pancreas at Hollywood Presbyterian Hospital from 1924 to July 1949*

No.	Year	Sex	Age	Duration of Symptoms	History of Trauma	How Diagnosed	Source of Material	Treatment	Site of Origin of Cyst in Pancreas	Days in Hospital	Pathologic Findings	Final Result	Final Diagnosis
1	1937	F	53	.....	No	Autopsy	Autopsy	None	Throughout pancreas	..	Many small retention cysts	Died from other causes	Multiple retention cysts of pancreas
2	1943	M	71	.....	No	Autopsy	Autopsy	None	Tail	..	4 cm. cyst, retention type	Died from other causes	Small retention cyst, congenital
3	1926	F	67	3 mo.	No	Roentgen study	Operation	Freed obstructed common duct from cyst wall; cyst left in	Head	..	Congenital 4 cm. retention cyst C. P. C. of liver	Lived	Congenital small retention cyst of pancreas
4	1943	M	41	5 wk.	No	At operation, emergency	Operation	Pseudocyst abscess marsupialized	Body	73	Inflammatory, necrotic, acute hemorrhagic pancreatitis with a 240 cc. abscess in pseudocyst	Lived	Pseudocyst with a 240 cc. abscess following acute hemorrhagic pancreatitis
5	1944	F	50	1 wk.	No	Roentgen study	Operation	Total excision of cyst and splenectomy (splenic artery accidentally cut)	Tail	32	True retention cyst with pancreatic tissue in walls	Lived	True retention cyst of pancreas
6	1944	M	46	3 hr.	Yes	At operation, emergency	Operation	Pseudocyst marsupialization	Head	13	Pseudocyst of pancreas containing 300 cc. dark bloody liquid	Lived	Pseudocyst of pancreas, hemorrhage
7	1945	M	53	3 mo.	No	Roentgen study	Medical examination	None	Head	15	Probable benign cyst 15.4 cm. in diameter	Lived	Probable benign cyst of pancreas from roentgen appearance
8	1948	F	46	6 mo.	No	Roentgen study	Operation	Total excision	Head	23	Fibrocystic adenoma of pancreas, 13 × 9 × 4 cm.; died on 22d postoperative day from 3 massive gastrointestinal hemorrhages; autopsy done; extensive fat necrosis and massive hemorrhage	Died	Fibrocystic multiloculated adenoma of pancreas
9	1949	F	73	2 yr.	Yes	Roentgen study	Operation	Total excision	Body	13	Pseudocyst of pancreas 16 × 15 × 13 cm.	Lived	Pseudocyst of pancreas

pseudocyst of the pancreas. The use of a preoperative abdominal anterior-posterior roentgenogram in conjunction with a barium meal commonly gives a clearcut picture in which the stomach or the transverse colon may be markedly displaced out of their normal anatomic relations with the other intra-abdominal viscera. Either one of these structures, and most commonly the stomach, may be compressed by a large homogeneous tumor shadow which commonly occupies the lesser omental sac and lies between the stomach and the inferior surface of the left lobe of the liver. If the patient gives a history of a tumor which apparently appears and disappears or if the examining surgeon finds such a tumor, this does not contraindicate a diagnosis of the presence of a pancreatic cyst. Hersche [37] in 1892 recorded an instance in which a cyst of the pancreas fluctuated markedly in size and at times even temporarily disappeared. Payr [38] cited a similar example in which a proved cyst of the pancreas disappeared and reappeared three times within two months. Judd, Mattson and Mahorner [14] mentioned 1 patient in whom a pseudocyst of the pancreas completely disappeared for a temporary period.

TREATMENT

Bozeman [39] in 1882 described one of the first cases of successful total excision of a large pseudopancreatic cyst. This cyst occurred in a woman 41 years of age, the wife of a physician residing in Texas. It was mistaken for an ovarian cyst on account of its size, the weight being 20½ pounds (9.4 Kg.). It was totally excised successfully, and the patient made an uneventful recovery. Willis and Budd [40] successfully resected a pseudocyst of the pancreas in a farmer aged 51. This cyst was stated to be the size of an orange. According to Willis and Budd, only 3 cysts were encountered at the Medical College of Virginia, and 1 of these was a pseudocyst. Judd [41] in 1921 reported the largest individual series of pancreatic cysts operated on until then, i. e., 41. No patient died at the time of operation. Five cysts were completely enucleated, and 3 additional patients were treated by the complete removal of the cyst's lining. Bouman [42] in 1922 performed

37. Hersche, J.: Operation einer Pankreascyste von seltener anatomischer Lagerung, Wien. klin. Wchnschr. **5**:727-728 (Dec. 22) 1892.

38. Payr, E.: Pankreascyste: seltene Topographie, Operation und Heilung, Wien. klin. Wchnschr. **11**:629-631 (June 30) 1898.

39. Bozeman, N.: Removal of a Cyst of the Pancreas Weighing 20½ Pounds, Med. Rec. **21**:46-47 (Jan. 14) 1882.

40. Willis, A. M., and Budd, S. W.: Pancreatic Cysts with Report of a Case, Surg., Gynec. & Obst. **20**:688-691 (June) 1915.

41. Judd, E. S.: Cysts of the Pancreas, Minnesota Med. **4**:75-82 (Feb.) 1921.

42. Bouman, H. A. H.: Pancreatic Cyst in Left Hypochondrium: Total Extirpation, Minnesota Med. **5**:697-706 (Dec.) 1922.

total extirpation of a large pancreatic cyst in the left hypochondriac region. Harrison and Cooper [43] in 1943 described a deliberate, successful excision of a pseudocyst of the pancreas in which the distal one half of the pancreas was removed with the cyst. Drainage of the pancreatic bed was not employed after the completion of the operation. Bernard, Dumet and Cotte [44] in 1924 added an additional instance of the successful total extirpation of a pseudocyst of the pancreas. Mousseau and Kling [45] cited an additional report of the successful total extirpation in 1948. Most investigators are agreed that, if possible, pseudocysts of the pancreas should be extirpated.

Some authors believe that the risk of total excision of a pseudocyst of the pancreas is formidable and that marsupialization or other indirect methods of drainage, either external or internal, constitute the treatment of choice. Oser [7] in 1903 reviewed the literature and found that 101 of 134 pseudocysts reported were operated on, with 81 patients recovering. Extirpation was done eleven times, with 2 deaths. Lahey and Lium [46] stated that the mortality from successful total excision of a cyst of the pancreas varied from 9.5 to 25 per cent and that if total excision failed the mortality might reach 55.5 per cent. Acuff [47] similarly warned that pancreatic surgical procedures carry an increased mortality rate.

Gussenbauer [48] in 1883, a pupil of Billroth, was the first surgeon reported to have performed external drainage by marsupialization of a pancreatic cyst, correctly diagnosed preoperatively. Chesterman [49] in 1943 was the first, according to the literature, to anastomose a cyst of the pancreas to the jejunum and thus institute this type of internal drainage. He successfully performed this operation on a 39 year old housewife, uniting the cyst through a 2 inch (5 cm.) stoma to the jejunum 2 feet (61 cm.) distal to the ligament of Treitz. This patient

43. Harrison, C., and Cooper, F.: Traumatic Pseudocyst of the Pancreas, J. Tennessee M. A. **36**:299-304 (Aug.) 1943.

44. Cited by Lahey, F. H., and Lium, R.: Cure of Pancreatic Fistula by Pancreatojejunostomy: Report of a Case with Review of the Literature, Surg. Gynec. & Obst. **64**:79-88 (Jan.) 1937.

45. Mousseau, L. P., and Kling, S.: Pancreatic Pseudocyst, Canad. M. A. J. **59**:550-554 (Dec.) 1948.

46. Lahey, F. H. and Lium, R.: Cure of Pancreatic Fistula by Pancreatojejunostomy: Report of a Case with Review of the Literature, Surg., Gynec. & Obst. **64**:79-88 (Jan.) 1937.

47. Acuff, H.: Management of Diseases of the Pancreas, South. Surgeon **13**:209-220 (March) 1947.

48. Gussenbauer, C.: Zur operativen Behandlung der Pankreas-Cysten, Arch. f. klin. Chir. **29**:355-359, 1883.

49. Chesterman, J. T.: Treatment of Pancreatic Cysts, Brit. J. Surg. **30**:234-235 (Jan.) 1943.

made an uneventful convalescence. All investigators warn that if an internal drainage of a pancreatic cyst to some portion of the gastrointestinal tract is contemplated the cyst must first be opened and its lining carefully scrutinized. If it is a papillomatous cystadenoma of the pancreas, such treatment will lead to disaster and the patient may succumb from an extensive carcinomatosis throughout the peritoneal cavity.

Hamilton [50] recorded an instance in which a pancreatic cyst had been marsupialized and this had been followed by an eight month postoperative period of profuse drainage. Radium was implanted along the drainage tract and in the cyst itself, and this treatment resulted within six months in the complete healing of the drainage tract and obliteration of the pancreatic cyst. Bickford [51] described several instances in which traumatic pseudocysts of the pancreas secondarily caused a pleural effusion. Poer and Stephenson [36] contended that most pancreatic cysts can be best treated by internal drainage of the cyst into the gastrointestinal tract. They recommended cystojejunostomy. Gordin [52] in 1937 presented a change of treatment of pancreatic cysts in which the cyst was opened and its lining was destroyed by the use of a sclerosing agent. Acuff [47] recorded a similar treatment.

CASE REPORT

This case is presented because in 306 reported instances of pseudocysts of the pancreas found in the available literature it is apparently the fortieth example of total excision.

History.—The patient was a white housewife, 73 years of age. Her chief complaint was a large tumor, of two years' duration, in the left upper quadrant of the abdomen which had increased in size, interfering with sitting and producing dyspnea. In 1929 she was in an automobile accident and received fractures of the left ninth through the twelfth rib in the anterior axillary line, after which she was unconscious for twelve hours. She was immediately hospitalized and was believed to have received an acute traumatic injury to some intraperitoneal viscus. Under general supportive medical measures and specific treatment for shock, she rapidly improved and went home at the end of one week. No intra-abdominal exploration was performed. A complete loss of function in the left shoulder joint for one and one-half years followed this accident.

Examination.—Her height was 5 feet, 3 inches (160 cm.) and her weight 134 pounds (60.8 Kg.). Her blood pressure was 204 systolic and 90 diastolic. There

50. Hamilton, C. S.: Prolonged and Profuse Postoperative Drainage of Pancreatic Cyst and Use of Radium, Surg., Gynec. & Obst. **35**:655-657 (Nov.) 1922.

51. Bickford, B. J.: Traumatic Pseudo-Cyst of the Pancreas with Pleural Effusion: Report of 2 Cases, Brit. M. J. **1**:1134-1135 (June 12) 1948.

52. Gordin, A. E.: Pancreatic Cysts Treated by Operation in Conjunction with Sclerosing Agent, Ann. Surg. **106**:1095-1096 (Dec.) 1937.

were moderate bilateral cataracts in the eyes, and the fundi showed moderate arteriosclerosis. The heart was enlarged to the left and downward. Palpation of the abdomen revealed a tender, fixed, hard mass in the left upper quadrant, 12.0 cm. in diameter. There was 50 per cent loss of the posterior rotation of the humerus at the left shoulder joint. The laboratory data were within normal limits.

Figure 2 depicts the principal abnormality found in a series of roentgenograms of the upper gastrointestinal tract.

Operation.—With the patient under spinal anesthesia, the upper region of the abdomen was explored through a transverse incision. A large pancreatic cyst

Fig. 2.—Preoperative anteroposterior roentgenogram. Barium meal shows marked displacement of the stomach laterally to the left and downward by a tumor mass lying in the area between the stomach and the left lobe of the liver.

was found presenting itself anteriorly through the gastrohepatic omentum. A cleavage plane was developed in the cyst wall. However, the cyst remained firmly attached to the posterior wall of the midportion of the stomach near the lesser curvature. This portion of the stomach was excised from the remainder of the stomach and left attached to the cyst wall. The cyst was removed without rupture. The capsule of the midportion of the body of the pancreas, from whence the cyst arose, was carefully reapproximated by imbricating over several of its layers. The opening in the stomach was then closed in the usual manner. The operative site was not drained. The anterior abdominal wall was reapproximated with a routine layer closure.

Fig. 3.—Surgical specimen. Gross appearance after 10 per cent formaldehdye fixation. Diameter after fixation was approximately 9.2 cm.

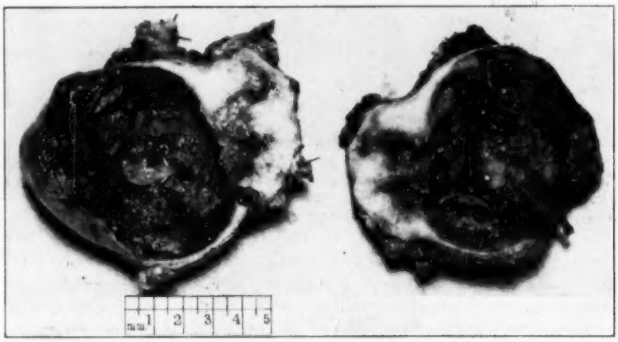

Fig. 4.—Surgical Specimen. Gross appearance after 10 per cent formaldehdye fixation and being cut in half. Note cystic portion, 7 cm. in diameter, containing partially organized old blood. Note solid area, measuring 5 by 3 by 3 cm. This area was yellowish and firm on palpation.

Postoperative Course.—The patient exhibited mild shock immediately after operation, which was successfully treated by a transfusion of 500 cc. of citrated whole blood. A Levin duodenal tube was inserted, and this was attached to a Chaffin-Pratt suction motor. This suction drainage was continued until the seventh postoperative day. She received two additional similar blood transfusions on the

Fig. 5.—Photomicrograph (× 400) of solid area shown in figure 4. Note fibrous tissue whirls and palisaded nuclei. Large blood vessels are seen. Special nerve tissue stains were negative.

third and sixth postoperative days. The height of the patient's postoperative fever was reached on the morning of the third postoperative day, when it was recorded as 100.6 F. by mouth. She was allowed out of bed on the eighth postoperative day. The incision healed normally without drainage. The patient was fully ambulatory on the tenth day and was dismissed home two days later. She was seen in my

office at weekly intervals (most recently on June 5, 1950), made an uneventful convalescence and stated on her most recent visit that she felt better than she had in many years.

Pathologic Findings.—Figures 3 through 6 show the principal details. The diagnosis was "traumatic pseudocyst of the pancreas."

Fig. 6.—Photomicrograph (× 1,100) of solid area shown in figure 3 under greater magnification. The fibrous tissue whirls and palisaded nuclei together with small collections of lymphocytes and dilated blood vessels are more clearly shown.

SUMMARY

A brief review is made of pseudocysts of the pancreas. The surgical literature indicates that while total excision of these pseudocysts remains the treatment of choice, it is still seldom performed. The history of 209,813 consecutive cases at the Hollywood Presbyterian Hospital has

been studied for the period between 1924 and July 1, 1949. Three pancreatic pseudocysts were found, or an incidence of 0.004 per cent. Only one pseudocyst was totally excised.

A case report is made of a successful total excision of a pseudocyst of the pancreas in a 73 year old woman. She made an uneventful convalescence, and her incision healed per primam. This pseudocyst, following an automobile accident, had a probable twenty year duration.

It is urged that, whenever possible, pseudocysts of the pancreas be completely excised, since prolonged hospitalization and persistent postoperative draining sinuses are thereby obviated.

TREATMENT OF POST-THROMBOTIC SYNDROME BY INTERRUPTION OF SUPERFICIAL FEMORAL VEIN

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ALTHOUGH current literature is replete with the various aspects of intravenous clotting and its role in pulmonary embolism, comparatively little stress has been placed on the equally important and disabling consequences of the disease in the affected extremity. These crippling sequelae are a familiar and most discouraging problem to every physician. The tense, swollen, discolored and painful limb is but a late stage of the inflammatory process which originated in the deep veins of the leg many years previously.[1] Thus in an analysis by Linton and Hardy[2] of 32 cases in which the extremities were involved, signs of venous insufficiency developed in 62 per cent within ten years; in 12.5 per cent they appeared the first year, and in 6 per cent they did not become manifest until after twenty years.

The rapidity and severity with which the picture of chronic venous insufficiency develops is largely dependent on the extent of the original phlebitis and the frequency of repeated episodes in the same limb. When thrombosis occurs only in superficial veins and relatively short segments, little if any permanent trophic changes occur, since collateral circulation is able to compensate for such minor degrees of obstruction. When thrombosis of a large venous trunk occurs, however, compensatory circulation is rarely adequate, and there are marked changes in the skin and the subcutaneous tissue.

Treatment of the far-advanced postphlebitic syndrome has been for the most part varied and unsuccessful. The long-suffering patient has often already had the questionable benefit of such treatment as prolonged rest in bed, elastic bandages, Unna paste boots, repeated ligation of

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1. Frykholm, R.: Pathogenesis and Mechanical Prophylaxis of Venous Thrombosis, Surg., Gynec. & Obst. **71**:307, 1940. Hunter, W. C.; Krygier, J. J.; Kennedy, J. C., and Sneeden, V. D.: Etiology and Prevention of Thrombosis of the Deep Leg Veins, Surgery **17**:178, 1945.

2. Linton, R. R., and Hardy, I. B.: Post-Thrombotic Syndrome of the Lower Extremity, Surgery **24**:452, 1948.

varicose veins and possibly a sympathectomy, with little or no improvement.

Various plastic procedures such as the radical excision of the ulcer and the surrounding indurated skin and subcutaneous tissue including the deep fascia, with the application of a split thickness skin graft, was recommended by Homans [3] in 1917. Brown, Byars and Blair [4] revived this method of treatment in 1936. However, long-term results were poor inasmuch as the abnormal venous circulation persisted.

In 1938 Linton [5] advised ligation of the communicating veins between the deep and superficial systems, along with interruption of the saphenous vein, in order that the increased pressure of the deep system would not be transmitted to the superficial veins. In 1939 Linton and Keeley [6] devised a method of treatment for the postphlebitic ulcer consisting of skin grafting the ulcer, followed by saphenous vein ligation, and six weeks later ligating the communicating veins on the medial or lateral side of the leg through a long incision extending from the upper third of the leg to the ankle. DeTakats and Fowler,[7] after a similar procedure, reported 17 good results among 23 patients; 6 patients, however, had recurrent ulceration within a year. A prolonged follow-up study on these patients was not available.

In 1943 Buxton and others [8] divided the superficial femoral vein on the hypothesis that recanalization always followed thrombosis. The resulting valve-deficient vein, they postulated, was incompetent, allowing retrograde flow of blood which furthered the development of edema, pigmentation and ulceration.

In a series of 21 patients reported in 1944, 16 showed definite improvement after the operation. Homans [9] and others, subscribing to this principle, advised interruption of the common femoral or common

3. Homans, J.: The Etiology and Treatment of Varicose Ulcers of the Leg, Surg., Gynec. & Obst. **24**:300, 1917.

4. Brown, J. P.; Byars, L. T., and Blair, V. P.: A Study of Ulcerations of the Lower Extremity and Their Repair with Thick Split Skin Grafts, Surg., Gynec. & Obst. **63**:331, 1936.

5. Linton, R. R.: The Communicating Veins of the Lower Leg and the Operative Technic for Their Ligation, Ann. Surg. **107**:582, 1938.

6. Linton, R. R., and Keeley, J. K.: The Post-Phlebitic Ulcer, Am. Heart J. **17**:27, 1939.

7. DeTakats, G., and Fowler, E. F.: Problem of Thrombo-Embolism, Surgery **17**:153, 1945.

8. Buxton, R. W.; Farris, J. M.; Meyer, C. A., and Coller, F. A.: Surgical Treatment of Long-Standing Deep Phlebitis of the Leg, Surgery **15**:749, 1944.

9. Homans, J.: (*a*) Deep Quiet Thrombosis in the Lower Limb, Surg., Gynec. & Obst. **79**:70, 1944; (*b*) The Late Results of Femoral Thrombophlebitis and Their Treatment, New Eng. J. Med. **235**:249, 1946.

iliac veins because of better collateral circulation at these levels. In 1946 Homans [10] advised concomitant ligation of the saphenous vein.

Linton and Hardy [11] in 1947 treated 34 patients with the post-thrombotic syndrome by ligation of the superficial femoral veins and stripping of the saphenous veins. Their results in the ulcerative extremities were excellent but only fair when edema was the principal complaint. In a subsequent report in 1948,[2] covering 84 post-thrombotic extremities, they stated that pain was completely relieved in 63 per cent and edema was markedly improved in 45 per cent. Ulcers were healed in 80 per cent; of the seven ulcers which did not heal, three responded after stripping of the underlying varicose vein.

The rationale of the combined treatment is that the venous blood is shunted into smaller deep veins which still have competent valves; further it prevents a reverse flow of venous blood down the deep veins from the superficial femoral veins, and it preserves the profunda femoris and the medial and lateral circumflex femoral veins as collateral channels for the return flow of the venous blood.[2]

In order better to understand this rationale, a review of the physiopathology and clinical course of the postphlebitic extremity is presented.

PHYSIOPATHOLOGIC CHANGES

The pathologic changes of thrombosis in the blood vessels are well known, but the cause of the initial clotting process in the veins remains unknown. It is beyond the scope of this paper to review the tremendous amount of investigative work that has been done along these lines. It is generally agreed, however, that intravenous clotting involves at least three factors, viz., disorders of the vein wall, changes in the blood itself and slowing of the venous return from the legs. In the chronic phase of the problem, we are concerned chiefly with the changes in the vein wall.

Edwards and Edwards [12] made a thorough study of experimental thrombophlebitis in dogs. They demonstrated the following changes in the post-thrombotic vein:

1. Mobilization of the organizing elements and fragmentation of the valve cusp. The most prominent changes occur at the junction of the cusp and the vein wall. Here a capillary which is normally small becomes dilated and proliferates. As the capillary network enlarges, it permeates the elastic tissue of the valve and thereby disrupts its struc-

10. Homans, J.: Diseases of the Veins, New England J. Med. **235**:163, 1946.

11. Linton, R. R., and Hardy, I. B., Jr.: Post-Thrombotic Sequelae of the Lower Extremity: Treatment by Superficial Femoral Vein Interruption and Stripping of the Saphenous Veins, S. Clin. North America **27**:1171, 1947.

12. Edwards, E. A., and Edwards, J. E.: The Effect of Thrombophlebitis on the Venous Valve, Surg., Gynec. & Obst. **65**:310, 1937.

ture. The infiltration of lymphocytes, microphages and fibroblasts further breaks up the architecture of the cusp.

2. Fibroblastic proliferation. At about the same time as the mobilization process gets under way, fibroblastic infiltration and organization of the clot begin. The agglutination of platelets on the injured endothelium and the deposition of leukocytes and fibrin produce the "white thrombus" which is adherent.[13] The earliest appearance of the fibroblast is seen at the angle of the valve cusp and vein wall, which is probably due to the proximity of the capillaries in this region. The organized tissue immediately fills the angle and binds the proximal part of the cusp to the vein wall, and eventually the entire cusp becomes fixed to the wall.

3. Recanalization. The organization of any clot is always associated with the process of vascularization. The proliferation of capillaries proceeds concurrently with the infiltration of the fibroblasts, so that by the time fragmentation of the valve cusp has been completed the capillaries are fused into communicating channels. The organizing process in the lumen thereby becomes penetrated by numerous intercommunicating channels which eventually coalesce, resulting in a valveless single lumen which may be large and therefore clinically important or small and relatively unimportant.

In either event, the return of blood from the extremity is aided by collateral circulation. When the collaterals are few in number, they are forced to dilate to accommodate the larger volume of blood. With dilation of the vessel to a diameter two or three times its normal size, it is evident that the valves will become incompetent. In the case of superficial collateral veins, there is an absence of firm support to the vessel wall, with the result that the vein dilates beyond its capacity for competent function and a varix appears.

Another explanation for the development of postphlebitic varicose veins is that given by Eger and Casper.[14] They theorized that since there are no valves in the inferior vena cava and the common iliac veins it is the role of the valves in the external iliac veins to support the column of blood when in the upright position.

In a study of 38 adult cadavers, these authors found absence of the valves in the external iliac and femoral veins in 37 per cent; there was unilateral absence of the valves in the external iliac arteries in 52 to 55 per cent, with only one valve in each of the femoral veins above the orifice of the internal saphenous vein. Hence, involvement of the femoroiliac segment with destruction of its single valve removes the only

13. Boyd, W.: Textbook of Pathology, Lea & Febiger, Philadelphia, 1947.

14. Eger, S. A., and Casper, S. L.: Etiology of Varicose Veins from an Anatomic Aspect, Based on a Dissection of 38 Adult Cadavers, J. A. M. A. **123**: 148, (Sept. 18) 1943.

support for the column of blood above the saphenofemoral valve, which places the latter structure under undue stress. With continued overburdening of the valvular mechanism, insufficiency results.

In addition to the valvular destruction, there is a perivenous reaction disseminated principally by the lymphatics accompanying the vessel.[15] Fibrinous exudation, hyperemia and fibroblastic infiltration result in a fibrous tissue coat which predisposes to edema by preventing dilation of the canaliculi in the organizing clot and by interference with normal lymph channels and lymph flow.[16]

The pathogenesis of edema is controversial and has been the subject of study by many investigators who have approached the problem from various aspects.

Parsons and McMaster[17] showed that in the absence of arteriolar pulsations there was practically no movement of lymph whereas in the presence of normal pulsation the lymph flow was rapid. They hypothesized that the vasoconstrictor impulses originating in the thrombosed segment of vein produce a vasospasm which results in a marked increase of intravenous pressure. Pressure readings up to 210 cm. of water have been reported by DeTakats and Quint.[18] This high pressure augments filtration and favors the increased transudation of fluid into the perivascular spaces. Also, the arteriolar spasm and diminished vascularity produce a relative anoxia of the capillary endothelium which favors increased permeability. Finally with the stagnation of lymph due to the absence of arteriolar pulsations, there is an accumulation of proteins in the perivascular fluid, and a vicious circle is set up in that the osmotic pressure of the interstitial fluid approaches that of the blood, with a lack of osmotic pull of fluid back into the venules.

This explanation is supported by Ochsner and DeBakey,[19] who advocated sympathetic block on the basis of abolishing vasospasm, which in turn decreases the venous pressure and the filtration pressure. The return of arteriolar pulsation following the block corrects the anoxia of the capillary endothelium and provides the pumping action for the return of lymph. These authors are of the opinion that even the edema of the

15. Homans, J.: Thrombophlebitis in the Legs, New Eng. J. Med. **218**:594, 1938.

16. (*a*) Jennings, J. E.: Choked Leg, Ann. Surg. **98**:928, 1933. (*b*) Ochsner, A., and DeBakey, M.: Postphlebitic Sequelae, J. A. M. A. **139**:423 (Feb. 12) 1949. (*c*) Homans.[9]

17. Parsons, R. J., and McMaster, P. D.: The Effect of the Pulse Upon the Formation and Flow of Lymph, J. Exper. Med. **68**:353, 1938; Effect of Pulse on Spread of Substances Through the Tissues, ibid. **68**:377, 1938.

18. DeTakats, G., and Quint, H.: Injection Treatment of Varicose Veins, Surg., Gynec. & Obst. **50**:545, 1930.

19. Ochsner, A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocain Block of the Sympathetics, Surgery **5**:491, 1939.

postphlebitic syndrome can be explained largely on the basis of vasospasm. In a much smaller group of cases (10 per cent), they feel, it may be due to incompetent valves or perivenous scar.[16b]

Holling, Beecher and Linton [20] expressed the opinion that edema is due to incompetent valves in the deep as well as the communicating veins of the lower region of the leg and is the result of sustained high pressures equivalent to the weight of a column of blood from the heart level to the level of the lower part of the leg. This pressure, being greater than the colloid osmotic pressure, produces an increased transudation of fluid into the perivascular spaces. While a normal lymphatic system and muscular contractions may prevent the accumulation of fluid, these two opposing factors are seldom present in the postphlebitic extremity.

Homans [21] and Zimmerman and DeTakats,[22] on the other hand, stated that the accumulation of fluid cannot be explained on the basis of filtration edema solely; when the capillary pressure rises above the osmotic pressure, there are also capillary stasis and anoxia of the endothelium which allow increased capillary permeability and loss of protein into the perivascular spaces. Later, a connective tissue reaction due to the persistence of a protein rich exudate strangles the lymph channels and causes a peripheral lymph block. This phenomenon has been observed in tissue excised in the Kondoleon operation, which shows dilated lymphatic vessels distal to an obstruction.

CLINICAL PICTURE

The first and most frequently encountered phase in the chain of sequelae is the appearance of edema. Its onset may follow immediately the acute stage of thrombophlebitis, although more commonly it tends to subside with the treatment of the acute process and does not again become manifest until the patient is ambulant. At first, swelling is noticeable at the end of the day and disappears after a night's rest.

The edema is subcutaneous and involves the foot and ankle region chiefly, although extension to the knee is not uncommon.

Coincident with the edema, congestion and cyanosis may occur. When edema has been present for a considerable time, irregular areas of brownish pigmentation due to the deposition of hemosiderin may appear. This is most noticeable above the ankle. Scratching or irritation of clothes seems to enhance pigmentation.

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20. Holling, H. E., Beecher, H. K., and Linton, R. R.: Study of the Tendency to Edema Formation Associated with Incompetence of the Valves of the Communicating Veins of the Leg, J. Clin. Investigation **17**:555, 1938.

21. Homans, J.: Thrombophlebitis of the Lower Extremities, Ann. Surg. **87**:641, 1928.

22. DeTakats, G.: The Management of Acute Thrombophlebitic Edema, J. A. M. A. **100**:34 (Jan. 7) 1933. Zimmerman, L. M., and DeTakats, G.: The Mechanism of Thrombophlebitic Edema, Arch. Surg. **23**:937 (Dec.) 1931.

Dermatitis in the form of eczema or erysipeloid infection is a most distressing sequel to persistent edema. Drinker and others [23] showed that edematous tissue favors the development of streptococcic infection. These organisms gain entrance to the skin through the fissures associated with epidermophytosis. The erysipeloid infection is characterized by chills, fever, burning pain and redness of the extremity.

Eczema of a chronic scaling type is seen in the regions of marked congestion or where ulcers have previously been present. Itching is common, and the severe forms of eczema develop largely as the result of persistent scratching. The sensitization of the skin to fungi has been emphasized [24] and may manifest itself by a vesicular type of eczema.

With edema of long standing, there occurs subcutaneous fibrosis, with encapsulation of the edema fluid in small lacunas of fibrous tissue, which prevents the absorption of the fluid through normal channels. The edema at this stage does not disappear when the patient is recumbent, and the skin takes on the appearance of hard brawny induration which is red or brownish. With increasing subcutaneous fibrosis the skin tends to shrink, causing further encroachment on the existent poor blood supply and predisposing to ulceration from minor trauma or irritation.

Ulcers commonly occur in the region of the ankle just above or below the medial malleolus. Infection is certain, and the resulting fibrosis in the margin further impedes healing.

The pain associated with this syndrome may be of several types. In the edematous phase, pain is of a dull aching character and appears on prolonged standing. It is probably due to venous congestion of the muscles and usually disappears within a short time after elevation of the limb.

Vasospasm may produce a throbbing type of pain in the calf, although more often the pain is not characteristic. Muscular cramps at night are also common in the spastic type.

The pain of ulceration and induration is frequently described as a burning pain not relieved appreciably by elevation. Secondary infection, with its accompanying cellulitis and lymphangitis, increases the severity of the pain and incapacitates the patient completely.

PHLEBOGRAPHIC STUDY

As an adjunct in determining the extent of the altered venous circulation, visualization of the venous network has proved helpful. After

23. Drinker, C. K.; Field, M. E.; Ward, H. K., and Lyons, C.: Increased Susceptibility to Local Infection Following Blockage of Lymph Drainage, Am. J. Physiol. **112**:74, 1935.

24. Thompson, K. W.: Studies on Relationship of Dermatomycosis to Ulceration and Gangrene of the Extremities, Yale J. Biol. & Med. **16**:665, 1944.

the work of Bauer,[25] phlebography was widely used in many vascular clinics.[26] However, the variable patterns of the normal phlebogram, the frequent compression of the deep veins by the tourniquet and the difficulty of interpretation of the abnormal gradually eliminated the procedure as routine in the work-up of vascular disease.[27]

Today, phlebography is generally reserved to establish the diagnosis of thrombophlebitis in the doubtful case, to determine the proximal extension of a thrombus or to aid in the differentiation between a primary syndrome of varicose vein and that due to incompetency of the deep venous system.[28] It is for the last purpose that my colleagues and I have utilized the procedure.

The existence of varicose veins poses a difficult problem of differential diagnosis. Are the varicosities secondary to old phlebitis or are they primary? Edema, pigmentation and ulceration are common to both. Ligation of the superficial femoral vein could hardly be expected to influence favorably the congestion and ulceration incident to primary varicose veins. Such treatment would be irrational and might even compromise an existing poor venous return. Nor could the ligation of secondary varicosities alone be expected to produce good results in the presence of a recanalized valveless femoral vein.

In an attempt to establish definite indications in such doubtful cases, we have recently utilized a technic of phlebography which will, under favorable conditions, demonstrate valvular damage and retrograde flow in the femoral vein. This technic is as follows: With the x-ray table in the upright position, the patient is instructed to stand in a lateral position with the involved limb placed against the Bucky diaphragm and extended forward from the uninvolved limb so that a true lateral view of the thigh and the lower region of the leg is obtained.

The region of the femoral trigone is now prepared with alcohol or merthiolate and the femoral pulse palpated. When the pulsation is located, approximately 10 cc. of 1 per cent procaine hydrochloride is injected in the area around the artery. A liberal infiltration of procaine

25. Bauer, G.: Venographic Study of Thrombo-Embolic Problems, Acta Chir. Scandinav. (supp. 61) **84**:1, 1940.

26. (*a*) Neuhof, H.: Venous Thrombosis and Pulmonary Embolism, Mt. Sinai Hospital Monograph no. 2, Grune and Stratton, N. Y., 1948. (*b*) Raymond, G. H.; Adams, G. T., and McCorriston, J. R.: Venography in the Normal and Pathological Leg, abstracted, J. Roentgenol. **52**:615, 1949. (*c*) Welch, C. E.; Faxon, H. H., and McGohey, C. E.: The Application of Phlebography to the Therapy of Thrombosis and Embolism, Surgery **12**:163, 1942.

27. Bull, D. W.: Phlebography of the Lower Extremity, S. Clin. North America **28**: 541, 1948.

28. Fine, J.; Frank, H. A., and Starr, A.: Recent Experiences with Thrombophlebitis of the Lower Extremity and Pulmonary Embolism: The Value of Venography as a Diagnostic Aid, Ann. Surg. **116**:574, 1942.

lessens the discomfiture of the procedure and at the same time tends to reduce any vascular spasm resulting from trauma to the artery or vein, and in the event of leakage of dye incident to the injection the local anesthesia will reduce the severe irritation to the soft tissues which iodopyracet injection (diodrast®) produces.

The patient is tested for sensitivity to iodopyracet injection by the instillation of 1 drop of the solution in the conjunctival sac. After five minutes, the conjunctiva is inspected and, unless there is a reaction, preparation is made for the injection of the solution. A 30 cc. syringe is filled with 35 per cent iodopyracet injection and fitted with a no. 18 gage needle. The needle is introduced into the previously anesthetized skin approximately 4 cm. below the inguinal crease and medial to the pulsation. The needle is advanced mesial and posterior to the artery, which is the usual position of the femoral vein at this level. A slight or moderate amount of resistance is encountered as the needle enters the vein wall, depending on the degree of fibrosis. The easy aspiration of blood confirms the position of the needle in the lumen, and the iodopyracet is injected rapidly while slight digital pressure is made above the site of injection. The roentgenograms are taken immediately at the completion of the injection, one of the thigh and one of the lower region of the leg.

Bauer [29] stated that the resulting phlebogram may be interpreted as follows: In instances of damage to the valves in the femoral vein retrograde flow of dye is manifested by the filling of the vein, which may appear widely dilated and tortuous along with numerous compensatory vessels similar to a superficial varicose vein (figs. 1 and 2). In a normal femoral vein the shadow cast is faint or absent, particularly in the distal portion of the vein, because of the central flow of the dye; where it is visualized, the outline is straight and relatively narrow, with only an occasional collateral branch being seen.

As has been emphasized by many investigators,[30] the thrombophlebitis starts below the knee in the great majority of cases. Frykholm,[1] Rössle [31] and Neumann [32] found that thrombosis originated distal to the profunda femoris in 85 per cent of cases, whereas there were no cases of solitary femoral thrombosis.

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29. Bauer, G.: Venous Thrombosis: Early Diagnosis with the Aid of Phlebography and Abortive Treatment with Heparin, Arch. Surg. **43**:462 (Sept.) 1941.

30. Bauer, G.: Footnotes 25 and 29. DeTakats, and Fowler.[7]

31. Rössle, R.: Ueber die Bedeutung und die Entstehung der Wadenvenenthrombosen, Virchows Arch. f. path. Anat. **300**:180, 1937.

32. Neumann, R.: Ursprungszentren und Entwicklungsformen der Beinthrombose, Virchows Arch. f. path. Anat. **301**:708, 1938; cited by Ochsner, A.: Surgery **17**:240, 1945.

Bauer [33] showed by phlebographic studies that femoroiliac thrombophlebitis starts in the deep veins below the knee in 90 per cent of cases and originates in the groin or pelvis in only 10 per cent.

In many cases, therefore, more pertinent information will be forthcoming if the phlebogram is obtained by injection of a superficial vein in

Fig. 1.—Needle in the lumen of the femoral vein. The distal portion of the vein, along with a collateral vessel, appears dilated and tortuous, indicating incompetency.

the foot distal to a tourniquet. Such changes as obstruction, minimal, or maximal recanalization of a thrombus, dilatation of the deep veins and varicosities of old phlebitic veins, as well as extensive collateral venous

33. Bauer, G.: Footnotes 25 and 29.

development, may be demonstrated by this technic. The phlebogram in chronic thrombophlebitis shows an extensive venous network. The normal slender vessels become thick trunks with multiple branches ramifying into the muscles and the subcutaneous tissue. Both the greater and the lesser saphenous veins appear enlarged and show numerous communicating channels.

Raymond and others,[26b] using a modification of Bauer's technic, found that contrary to general belief the deep circulation of the lower

Fig. 2.—Filling of some superficial varicose veins which are secondary to the thrombophlebitic process.

extremity follows a fairly consistent pattern in normal subjects. Any deviation from the normal as evidenced by lack of filling of a part or all of the deep veins and a filling of the superficial system is considered pathologic. In our experience with the method, such well defined conclusions are seldom justified.

Our early enthusiasm for the retrograde injection method has also waned in view of the technical difficulties encountered in obese patients

and in instances of excessive perivenous fibrosis. Nevertheless, the demonstration of the degree and type of pathologic change in the suspected case justifies its use when physical factors are favorable.

Definite valvular pathologic changes in the femoral segment would appear to be the only rational indication for ligation of superficial femoral veins.

Ligation of the vein in cases in which the phlebitic process was limited to the lower part of the leg may be expected to yield poor results, since interruption of the normal-valved femoral vein would only partially influence the flow of blood in an incompetent deep vein, with its numerous communicating veins.

RESULTS

Ligation of superficial femoral veins was performed on 10 patients with the post-thrombotic syndrome (table). In 2 patients, however, it was performed too recently for them to be included in this survey.

Although the immediate results in all 10 patients were satisfactory, with diminution in edema, lessening of pain and healing of ulceration in 2 cases, these effects could also be accounted for by rest and general hospital care given incidental to surgical treatment.

Follow-up on at least 4 of 7 patients after six to eight months indicates that surgical intervention was definitely helpful. The most troublesome and least responsive condition to treat is edema. Only 3 of the 7 patients showed improvement in this respect. Linton and Hardy [2] reported relief of edema in 45 per cent of their patients and stated that many of the remaining 55 per cent will ultimately be able to discontinue the use of elastic stockings. Relief of pain and improvement in stasis dermatitis, on the other hand, was gratifying.

One ulcerative limb which healed after ligation broke down, with recurrence of the lesion in six months. Two ulcers have remained healed. Two other patients considered to have poor results showed no further deterioration of the extremity as a result of surgical treatment.

In a series of 64 ligations of superficial femoral veins performed at Veterans Administration Hospital, Wood, Wis., since 1946 for both acute and chronic thrombophlebitis there has been but one complication, that of gangrene of the toes from persistent vasospasm. A similar complication has been reported by Sarnoff,[34] and acute venous congestion necessitating wide fascial incision has been reported by Dennis [35] and by Homans.[9b]

34. Sarnoff, J.: Gangrene of Both Legs Following Femoral Vein Ligation, New York State J. Med. **48**:1480, 1948.

35. Dennis, C.: Disaster Following Femoral Vein Ligation for Thrombophlebitis: Relief by Fasciotomy; Clinical Case of Renal Impairment Following Crush Injury, Surgery **17**:264, 1945.

In capable hands, interruption of the femoral vein is a safe procedure attended by insignificant mortality and morbidity.

Although this small group is of no statistical significance, Linton and Hardy stated that in over 3,000 ligations performed at the Massa-

Ligation of Superficial Femoral Veins in 10 Patients

Patient	Age	Physical Findings	History	Operation	Pathologic Process	Immediate Results	Follow-Up
S. B. C.	50	Edema, pain; stasis dermatitis; varicose vein	Thrombophlebitis, 1944	Superficial femoral ligation; varicose vein ligation	Recanalized (large lumen)	Pain relieved	Not available
A. F.	60	Edema, bilateral; pain in calves; pigmentation	3 episodes of thrombophlebitis, 1947 and 1948	Right superficial femoral ligation; left common femoral ligation	Partially recanalized vein, right; occlusion common femoral, ligation	Pain relieved, swelling diminished	Satisfactory; working
C. F. K.	48	Throbbing pain in left leg; swelling of foot and ankle; night pain in left calf	Indefinite history of thrombophlebitis	Left superficial femoral ligation	Patent vessel, periphlebitic thickening	Complete relief of pain, edema unchanged	Working
L. S.	60	Pain in left leg 1 mo.; swelling, both ankles; varicose veins (left)	Thrombophlebitis, 1929	Superficial femoral ligation	Marked periphlebitic scarring with recanalized vessel (large lumen)	Pain relieved; edema diminished	Satisfactory; not working
N. O.	59	Pain in left leg 9 mo.; varicose veins, bilateral; ulcer of left ankle; edema of both ankles	Indefinite history	Left superficial femoral vein ligation	Patent vein completely recanalized	Ulcer healed; pain relieved	Not able to work; recurrence of ulcer
A. J. N.	62	Stasis dermatitis of right leg; varicose vein, bilateral; edema, right leg	Thrombophlebitis, 1948	Common femoral ligation	Minimal recanalization of thrombus (small lumen)	Pain relieved; swelling lessened	Satisfactory; not working
D. B.	57	Pain in both legs 2 yr.; pigmentation, edema (4 plus) bilaterally; ulcer, left ankle	None	Left superficial femoral ligation	Recanalized, both vessels; moderate lumen	Ulcer healed; edema lessened, pain relieved	Edema present, pain lessened; ulcer healed
L. A.	58	Edema; pain in both calves	2 episodes pulmonary infarction 8 and 6 mo. previously	Right superficial femoral ligation; left superficial femoral ligation	Partially recanalized; complete recanalization with periphlebitis	Moderate pain relief	Unsatisfactory; return of pain and edema
A. H. B.	37	Pain in left leg; ulcer, left leg; varicose veins	Thrombophlebitis following sodium morrhuate injection for varicose veins 5 yr.	Superficial femoral ligation; ligation of varicose veins	No apparent involvement	Ulcer healed; diminished edema	None
W. L. H.	31	Pain in calf; swelling in left leg; stasis dermatitis; ulcer since 1944	Thrombophlebitis after herniorrhaphy 7 yr. previously	Common femoral ligation	Minimal recanalization of thrombus (tiny lumen)	Pain and dermatitis relieved	None

chusetts General Hospital the incidence of postphlebitic sequelae has been minimal.[2]

Six of our patients were over 55 years of age, which brings up the question of the role of arteriosclerosis in this syndrome. Impairment of the arterial circulation coupled with a certain amount of vasospasm

incident to old thrombophlebitis would certainly contribute to the persistence of trophic skin changes in spite of ligation of superficial femoral veins. For this reason, Buxton and Coller [36] have limited selection of their patients to those below 55. Our observations would appear to support this selectivity. However, in a veterans' hospital a great number of cases of venous insufficiency are found in the older age groups, and many of the men have had repeated forms of treatment over a period of years. Hence, any salvage among this group must be considered well worth the minor risk of surgical intervention.

SUMMARY

A review of the physiopathologic changes and clinical findings in long-standing thrombophlebitis is presented, and a method of retrograde phlebography to show the extent and type of phlebitic process is introduced.

Ten patients who have undergone ligation of superficial femoral veins have been studied. The long-term effects of the procedure have not as yet been observed, although a follow-up covering six to eight months indicates that results are good in 55 per cent of the patients, including those with arteriosclerotic peripheral vascular disease. Such results, although admittedly not good statistically, would appear to justify continued use of the procedure in a disease which has failed to respond even in a small proportion of cases to the many forms of treatment prescribed.

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36. Buxton, R. W., and Coller, F. A.: Surgical Treatment of Long-Standing Deep Phlebitis of the Leg: A Supplementary Report, Surgery **18**:663, 1945.

ALLERGIC REACTIONS FOLLOWING THE INTRAVENOUS INJECTION OF CORN SUGAR (DEXTROSE)

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IN THE past, reactions following the intravenous administration of solutions have been interpreted principally as being due to pyrogen contamination. In a recent review of this subject, Rademaker [1] stated that the care of glassware and tubing remains the predominating factor in the production of reactions. Speed shock has also been considered as a cause.

However, in spite of the most careful attention in respect to the control of pyrogens and the regulation of the speed of administration of solutions, there remains an unexplained irreducible residue of reactions. The paradox persists that solutions and tubing prepared from lots which have not been suspected in the majority of patients are incriminated as the most probable cause of reactions in an occasional instance. This type of observation suggests that the individual patient may be reacting abnormally to the injected material; the most plausible explanation for an individual idiosyncrasy is an allergic reaction.

In view of the fact that allergic responses to injected materials have received little emphasis in this connection, a critical review of this possibility seems indicated. The discussion will be limited to reactions following the intravenous administration of 5 per cent solutions of dextrose. The question of similar reactions following injections of sucrose will be considered in another communication.[2]

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1. Rademaker, L.: Reactions to Intravenous Administration of Solutions, J. A. M. A. **135**:1140 (Dec. 27) 1947.

2. Randolph, T. G., and Rollins, J. P.: Allergic Reactions from the Ingestion or Intravenous Injection of Cane Sugar (Sucrose), J. Lab. & Clin. Med., to be published.

It is not generally appreciated by physicians that dextrose available for parenteral administration is prepared from the simple hydrolysis of cornstarch, so completely has the term been dissociated from the source material employed in its manufacture. Sensitivity to corn occurs at least as often as sensitivity to wheat [3] and in our experience is slightly more common.[4] Furthermore, we [5] have recently shown that crystalline sugars prepared from corn starch may cause intense and unmistakable allergic reactions when ingested by certain persons highly sensitive to corn. The rapidity of the onset and the severity of such clinical reactions suggest that the sugar is allergenic in the form administered rather than in some form occurring after ingestion. Of further interest in the matter of the specificity of such reactions is the fact that alpha-*d*-glucose prepared from beet sucrose fails to produce symptoms when ingested by the patient who is sensitive to corn and who reacts specifically to corn sugar; conversely, glucose prepared from beet sucrose will produce allergic reactions when ingested by patients known to be sensitive to beets.[6]

Interest in studying this problem arose from observations in several patients highly sensitive to corn that the clinical features following the intravenous injection of 5 per cent dextrose were similar if not identical to the reactions following the ingestion of sugars of corn origin. Consequently, several allergic patients known to possess a high degree of corn sensitivity were selected for the experimental injection of corn sugar (dextrose).

CASE 1.—E. M., a physician's wife aged 22, has previously been reported on.[8] She was first seen in 1946, giving a history of intermittent asthma since childhood, acute gastrointestinal upsets beginning at the age of 15 and the onset of perennial allergic rhinitis and chronic fatigue at the age of 19 years. In view of the subsequent diagnosis, it is of interest to note that she had been subject to chronic colds associated with daily elevations in temperature and tender swollen cervical glands occurring in the months of July and August for the preceding two years. These acute reactions were not associated with high pollen or fungus counts and were not explained on the basis of infectious mononucleosis or other apparent causes.

Specific treatment for sensitivity to house dust failed to afford satisfactory relief of her symptoms. Food diary evidence revealed attacks of sneezing, pruritus and urticaria following meals containing corn on the cob. An individual food test with corn was followed by abdominal cramps, generalized itching, marked fatigue

3. Rinkel, H. J.; Randolph, T. G., and Zeller, M.: Food Allergy, Charles C Thomas, Publisher, Springfield, Ill., to be published.

4. Randolph, T. G., and Yeager, L. B.: The Incidence of Allergy to Major Foods, J. Lab. and Clin. Med. **32**:1547, 1947.

5. Randolph, T. G., and Yeager, L. B.: Corn Sugar as an Allergen, Ann. Allergy **7**:651, 1949.

6. Randolph, T. G., and Rollins, J. P.: Beet Sensitivity: Allergic Reactions from the Ingestion of Beet Sugar (Sucrose) and Monosodium Glutamate of Beet Origin, J. Lab. & Clin. Med., to be published.

and a recurrence of the tender, swollen anterior cervical glands. The complete elimination of corn products and the continuation of dust therapy afforded complete relief of symptoms. Corn sugar seemed to be particularly effective in producing severe allergic symptoms; its inadvertent ingestion on several occasions was invariably followed by an acute allergic response; this highly specific reaction aided us in determining whether a given product contained sugar of corn or some other origin.

As previously described,[5] she reacted with sharp clinical symptoms after the ingestion of U. S. P. dextrose. However, when the dextrose was injected intravenously, with 0.5 Gm. in 1.0 cc. solution and subsequently with 10.0 Gm. in 20.0 cc. solution, a symptom response failed to develop. From this preliminary evidence we were led to believe that the intravenous injection of corn sugar might be tolerated even by a person exquisitely sensitive to corn. As a result of this experience no further tests were made for a period of two years or until case 2 (M. W.) was encountered. In as much as all subsequently tested patients reacted with symptoms of intolerance after the intravenous injection of corn sugar, the opportunity presented itself to reexamine this patient in August 1949. She had remained highly sensitive to corn during the interim.

Twenty-five cubic centimeters of 5 per cent dextrose (Baxter) was injected intravenously by a pyrogen-controlled technic to be described subsequently. Twelve minutes after the completion of the injection a pulling and drawing sensation of the nuchal muscles developed which rapidly spread to the right frontal area. The patient's headache increased in intensity and became associated with pain and tenderness in the region of the mastoid process bilaterally. Generalized aching of her extremities then developed, suggesting the prodromal symptoms of grip. These symptoms, in addition to residual fatigue, persisted for two days.

She reported four days later, having been symptom free for the preceding two days, and submitted to the intravenous injection of 20 cc. of 50 per cent dextrose (Eli Lilly & Company), an exact duplication of her test performed three years earlier which had not been associated with reactive symptoms. After twenty minutes she complained of a bilateral temporal headache, followed in three minutes by aching painful sensations in the region of the mastoid processes. The generalized aching sensations of her extremities previously noted developed, and she also complained of tenderness of the abdominal wall of the type seen in other patients with a condition diagnosed as allergic myalgia[7] and of marked stiffness of the back and the posterior region of the neck. Generalized muscle aching and extreme fatigue persisted for the following two days.

EXPERIMENTAL OBSERVATIONS

Because of the increasing clinical evidence of intolerance to intravenous injections of corn sugar in patients sensitive to corn, an experimental study of this problem was started in early 1948.

In all instances a constant control of pyrogen factors was maintained by employing only freshly prepared solutions supplied through the courtesy of the Baxter Laboratories. The technic to control pyrogen reactions to be described met the approval of this firm. In each case

7. Randolph, T. G.: Allergy as a Cause of Nuchal Myalgia and Associated Headaches, Arch. Otolaryng. **50**:745 (Dec.) 1949; Allergic Myalgia, to be published.

pyrogen-free distilled water, supplied by the Baxter company, was employed in rinsing and sterilizing the equipment. A single chemically clean large glass syringe and a 24 gage needle were employed for the injection. The syringe, needle and container in which the equipment was boiled for ten minutes were each rinsed seven times in successive samples of distilled water prior to sterilization. The syringe with needle attached was filled and emptied five times with the solution which subsequently was to be injected. The syringe was then loaded and the injection made in the antecubital vein, the site having been prepared with alcohol. The material (usually 25 cc.) was injected over an average period of seven minutes.

The selected patients were aware of the fact that they were to receive an intravenous injection of some type of sugar solution, but they did not know in advance of the injection or for several hours thereafter whether they were receiving sugar of corn origin or sugar of cane origin. Each patient was prepared for the injection by the absolute avoidance of all sources of corn and cane for at least four days prior to the experimental injection. The instructions for avoidance of corn are listed elsewhere.[3] Patients were resting comfortably in the sitting position at the time of the injections. In each instance, the subject had not partaken of any food for at least five hours and had been under clinical observation for at least thirty minutes prior to the experimental injection, the severity and incidence of any allergic manifestations having been recorded per unit of time thirty minutes prior to and ninety minutes after the intravenous administration. A total leukocyte count was taken immediately prior to and at twenty, forty and sixty minutes after the injection. In some instances the leukocyte observations were continued for longer periods. The incidence of subjectively and objectively measurable allergic symptoms was recorded by a technician trained in the detailed technic of the individual food test for the diagnosis of food allergy.[3]

CASE 2.—M. W., a dietitian and the wife of a physician, aged 30, had been subject to episodes of nausea, vomiting and diarrhea for eight years, severe fatigue, generalized muscle soreness and headaches for three years and unexplained urgency and frequency of urination for three months prior to her initial visit in April 1948. Multiple daily injections of codeine had been necessary to relieve her constant headaches, posterior cervical myalgia and generalized aching.

A review of her treatment in hospitals in respect to the intravenous administration of corn sugar was revealing. The patient had been admitted to a general hospital in 1942 with a diagnosis of nausea of pregnancy and irritable colon, and she received her first three injections of 5 per cent dextrose in sodium chloride solution intravenously on successive days. Two hours after the third injection was started she complained of the onset of a chill and severe pains in the right lower region of the chest and the midback; at three hours a sharp increase in nausea and diarrhea developed; at three and one-half hours more severe chills were followed by an elevation in temperature to 100.4 F. At seven hours her temperature reached 102 F.

and she complained of severe abdominal cramps. The following morning her temperature reached a maximum of 102.4 F., her nausea was much more severe and she had more persistent vomiting. She remained extremely fatigued, restless, nervous and irritable for the following two days and then recovered, having received no further venoclyses.

After her admission to a general hospital for delivery three months later, 1,000 cc. of 5 per cent dextrose was again given by vein. According to the nurses' notes, she immediately complained of severe gas pains, and subsequently retching, vomiting and generalized urticaria developed.

The patient was admitted to an army hospital in 1946 for the removal of a cervical polyp but was kept under observation for a month in an attempt to explain her continual muscle aching and severe gastrointestinal symptoms. A dextrose tolerance test was followed almost immediately by the onset of severe nausea, vomiting and anuria; this reaction was treated by the administration of 1,000 cc. of 5 per cent dextrose intravenously. Violent retching and vomiting reached a crescendo during the period of administration and required three days to subside.

In July 1947 she was again hospitalized for a dilation and curettage. The oral administration of codeine was followed by nausea and vomiting, but these symptoms were sharply accentuated during and after the period when she was receiving 1,000 cc. of corn sugar intravenously. Her initial febrile reaction of 100.2 F. again developed. Dextrose was injected the next day and was followed by a sharp increase in her temperature and the gastrointestinal symptoms.

In January 1948 she was hospitalized because of the complaint of burning in the region of the urinary bladder and anuria. One thousand cubic centimeters of isotonic sodium chloride solution was administered intravenously in the absence of any increase in symptoms and was followed by urination for the first time in twenty-four hours. Later the same day she received 1,000 cc. of 5 per cent dextrose by intravenous drip; this was followed by an immediate increase in dysuria and bladder tenesmus and by the development of intense nausea and vomiting during the period of administration, the last being the initial gastrointestinal symptoms at the time of this admission to the hospital. In the absence of further intravenous alimentation, these symptoms gradually subsided.

In early April 1948, during one of her periodic recurrences of severe headache, posterior cervical myalgia and anorexia, intravenous dextrose therapy was started as a nutritional measure but was immediately followed by an increase in the severity of retching and vomiting. The venoclysis was repeated the following day, and during the period of administration there developed a sharp recurrence of vomiting, headache and myalgic pains in the neck and the upper part of the arms. In the absence of further intravenous therapy the patient was better the following day and ate the first food for several days, consisting of corn sugar, milk and potatoes (she was subsequently found to be highly sensitive to these foods.) After this meal her symptoms were accentuated to the point where it seemed advisable the following morning to administer more corn sugar intravenously; this was promptly followed by the development of intense pain in the head and neck and a recurrence of vomiting and dysuria. On April 15 she was given 1,000 cc. of 5 per cent dextrose in the morning and again in the afternoon, and similar venoclysis was repeated on each of the following three days. Progressive weakness, nausea, vomiting, dysuria, headache and generalized muscle aching ensued. She was then brought by stretcher 400 miles (643 kilometers) to Chicago, arriving in an extremely debilitated condition. She was immediately placed on a dietary program excluding all corn products. Various other items of the diet not previously ingested during the preceding four days were

returned one by one in individual food tests.[8] Incompatible foods were eliminated as detected, and compatible foods were retained in the diet. By the end of the second hospital day her intense dysuria, urgency and frequency began to improve, and by the end of a week she was ambulatory and fairly comfortable.

A month later she was given 25.0 cc. of 5 per cent dextrose intravenously, the technic, pyrogen control and material previously outlined being employed. Three minutes after the injection was started she complained of the onset of a dull aching pain in the right posterior side of the neck coincident with the development of flushing and perspiration. The initial chill with observable gooseflesh was noted at thirteen minutes. Nasal stuffiness and myalgic pains across her shoulders appeared after fifteen minutes. Urgency, frequency and burning in the region of the urinary bladder recurred at thirty minutes; these symptoms had been absent for the previous three months. All symptoms increased in severity during the following hour, and progressive nausea and abdominal distress occurred for the first time. She remained extremely weak, tired and nervous for the remainder of the day and still had some residual fatigue, tenseness and nervousness the following day.

Several days later the patient was induced to repeat the corn sugar test but instead was given 25 cc. of isotonic sodium chloride solution. Under identical conditions symptoms failed to develop.

CASE 3.—E. R., a housewife aged 54, had been subject to intermittent headaches for fifteen years and continual headaches during the past decade associated with constant dizziness. When first seen in 1946 she also complained of a debilitating degree of weakness, alternating constipation and diarrhea and chronic dermatitis of her hands.

House dust therapy was helpful in partially controlling her symptomatology. She was shown to have a widespread allergic reaction to foods as indicated by the precipitation of acute clinical reactions following individual tests of food ingestion.[8] Corn proved to be one of her most troublesome foods. With the continuation of house dust therapy and the complete avoidance of corn and other incriminated foods her symptoms were effectively relieved for a period of several months except when she inadvertently encountered a source of one of her food allergens.

Sensitivity to corn existed to such a degree in this case that on several different occasions the patient reacted with intense symptoms to the ingestion of small amounts of corn employed as excipients in pharmaceutical tablets.[9] On several different occasions the ingestion of dextrose encountered by accident in commercially prepared foods has also been followed by the immediate production of acute allergic reactions. This degree of specific sensitivity to corn has persisted for the past two and one-half years in spite of diligent efforts to avoid its ingestion.

On June 6, 1949, she submitted to an intravenous injection of 5 per cent dextrose, administered in accordance with the previously described technic. Six minutes after the completion of the injection of 25 cc. of the dextrose in water she complained of drowsiness, repeated sniffling and tenseness of the muscles of the extremities. At twenty minutes she started coughing and raised copious amounts of phlegm, noted excessive lacrimation and complained of pulling and drawing sensations in the

8. Rinkel, H. J.: Food Allergy: II. The Technique and Clinical Application of the Individual Food Test, Ann. Allergy **2**:504, 1944. Randolph, T. G., and Rawling, F. F. A.: Blood Studies in Allergy: V. Variations of Total Leucocytes Following Test Feeding of Foods, An Appraisal of the Individual Food Test, Ann. Allergy **4**:163, 1946.

9. Randolph, T. G.: Allergic Reactions to So-Called "Inert Ingredients" (Excipients) of Pharmaceutical Preparations, Ann. Allergy, to be published.

posterior cervical muscles. These symptoms increased progressively in severity, and after forty minutes a generalized severe headache, multiple scotomas and hoarseness developed. Her headache and other constitutional symptoms of weakness and generalized muscle aching incapacitated her for the remainder of the day and persisted throughout the following day. On the second day she also complained of soreness of her eye balls, difficulty in focusing her eyes, general muscular incoordination, impairment of memory and a definite tendency toward stuttering and aphasia. These symptoms associated with extreme fatigue gradually tapered off during the following two days, so that by the evening of the fourth day she was again symptom free.

CASE 4.—M. R., aged 37 and the wife of a physician, had been subject to perennial nasal allergy for the past decade, with intermittent nasal obstruction and other more acute exacerbations characterized by soreness of her throat and enlargement of the anterior cervical glands. She remained subject to severe frontal headaches associated with intense pulling and drawing sensations of the posterior cervical muscles and vomiting. For many years she had also complained of periods of acute melancholia superimposed on a background of chronic low grade depression and despondency associated with continual fatigue and listlessness which made it exceedingly difficult to carry on her daily work. Physical examination was noncontributory except for the presence of pale, boggy nasal mucous membranes. Although she received considerable benefit from house dust therapy, she continued to complain of her constitutional symptoms.

She was found to be sensitive to wheat, corn, rye, milk, eggs and pork as a result of acute symptom reactions occurring in the course of individual food tests with major articles of diet. Only the details of her sensitivity to corn will be reported at this time. On the avoidance of all sources of corn for four days prior to an individual food test with it, she reported a decided improvement for the first time in many months. Thirty minutes after the second feeding of corn meal gruel and corn sugar severe chills and headache developed, which persisted for the remainder of the day.

Two months later she submitted to the injection of 25 cc. of 5 per cent dextrose intravenously. Seven hours later she first noticed an area of angioedema of the face. Although she passed the night uneventfully, she remained unusually tired and depressed throughout the following day.

Ten days later she was given 500 cc. of 5 per cent dextrose intravenously over a period of ninety minutes. Seventy minutes after the intravenous injection was started she complained of a mild frontal throbbing type of headache which at first was present in intermittent waves but which became constant thirty minutes after the completion of the fluid administration. At this time the head pain increased in intensity and became associated with pulling, drawing and aching sensations in the area of the cranial attachments of the posterior cervical muscles, nasal stuffiness, excessive gas, belching and depression and despondency. An intense headache persisted for the remainder of the day. The following morning she felt "doped," dull and extremely tired. She "remained in a fog" throughout the day, carrying on with her routine work only with great effort because of the dulled mental acuity and aching of the muscles of the posterior region of the neck and the upper part of the back. By the second day the baseline condition existing prior to the test had returned and she claimed that she was able to accomplish more in an hour than she had done all the previous day.

CASE 5.—A. N., an engineer aged 41, had been subject to recurrent headaches of increasing severity and frequency during the two years prior to his initial visit in February 1949. Individual attacks were characterized by a sense of pressure

over the right frontal area, scotomas, inability to focus his eyes normally, nausea and profuse diarrheic stools. There had been considerable pulling and tautness of the posterior cervical muscles occurring to some extent at all times but sharply accentuated during a headache. He also remained chronically tired and "groggy" between acute headaches. Progressive rhinitis had been a major symptom during the past two years.

Repeated physical examinations had failed to reveal significant abnormalities. Although there was no history of inhalant allergy, the patient reacted positively to house dust on cutaneous and intracutaneous testing. Specific therapy with house dust on two occasions resulted in the production of an accentuation of the cervical myalgia and a moderately severe headache. Dust therapy at a slightly lower dosage level materially reduced the severity of the nuchal pain and fatigue, but he remained subject to intermittent or continuous headache.

Individual food tests were then performed with the major foods of his diet and all gave negative reactions with the exception of the test with corn. The avoidance of this food prior to experimental feeding was associated with cessation of his continual headache for a period of two days prior to the test, and the ingestion of corn meal and corn sugar was followed by the delayed accentuation of his rhinitis and the development of a severe headache associated with fatigue and nuchal myalgia.

With the continuation of dust therapy and the avoidance of corn, he reported complete relief of his formerly troublesome symptoms for a period of three weeks. He then submitted to the injection of 25 cc. of 5 per cent dextrose intravenously, which was administered over a period of seven minutes. Five minutes after the completion of the injection he complained that his face felt warm; the validity of this observation was confirmed by the objective evidence of increased flushing of his face. The subjective evidence of chilliness was reported at ten minutes, which progressed rapidly to the development of a true chill associated with the presence of gooseflesh and shivering. At twenty minutes he reported the simultaneous occurrence of pressure in the frontal area and drawing sensations of the right posterior cervical muscles; this was followed by the progressive development of head pain, huskiness of his voice, increased phlegm in his throat and excessive clearing of his throat. Dull headache, nuchal symptoms and intermittent chilliness persisted for the remainder of the day. By the following morning all symptoms had subsided except for residual fatigue and tension in the right posterior cervical muscles.

During the height of this reaction there was increased tonicity and tenderness of the right posterior cervical muscles as determined by palpation of this area prior to and after the induction of the headache.

COMMENT

Five patients were selected for this presentation because of their high degree of specific sensitivity to corn sugar both on ingestion and as a result of intravenous injection. The first patient was not found sensitive to the intravenous injection of corn sugar when this was first tried but subsequently exhibited this reaction. The second person was aware of her intolerance to the intravenous injection of dextrose prior to a knowledge of the existence of corn sensitivity, not being aware that dextrose was of corn origin. The fourth patient, although highly sensitive to corn clinically, showed only a mild questionable reaction after the

intravenous injection of 25 cc. of dextrose but showed a sharp clinical response in association with the administration of 500 cc. of corn sugar. The final patient requested the test of the intravenous administration of corn sugar, knowing of his high degree of corn sensitivity, in order to ascertain his possible reaction in the event of a future surgical emergency. Three other patients highly sensitive to corn were also subjected to identical tests, and in each similar evidence of reaction developed after the intravenous administration of corn sugar. It should be pointed out that each of these persons was known to be sensitive to the ingestion of corn sugar but that none of them was aware of this fact until a specific diagnosis had been made. This is not a unique finding, for as a general rule a person sensitive to corn is usually unaware of it, and even though corn allergy might be suspected, we have never found a person who was able to remove the sources of corn from his diet in the absence of specific instructions of how to do so.

We have demonstrated that the intravenous injection of corn sugar (dextrose) is not always innocuous per se, for certain allergic persons highly sensitive to corn react to this procedure by the development of allergic symptoms. The symptoms observed in these reactions are more apt to be in the nature of constitutional manifestations of allergy, recently reviewed,[10] rather than the more classic allergic responses such as asthma or rhinitis. Although relatively severe symptoms of the type described may occur, it seems probable that even less acute clinical responses might be more common. In many instances the majority of such minor responses are probably attributed to other factors and not recognized as possible allergic reactions.

For these and other reasons the actual incidence of allergic type of reactions following the intravenous injection of corn sugar is difficult to appraise. From the standpoint of the incidence of corn sensitivity, one might expect it to be a fairly common explanation for reactions following the intravenous injection of dextrose, for in the private practice from which these persons were selected, 1 in 5 new patients is found to be clinically sensitive to corn and the majority of this group react with allergic manifestations after the ingestion of corn sugar or syrup. Rinkel,[11] who was the first to emphasize the clinical significance of corn allergy, recently tabulated a series of 200 patients studied for food allergy, finding 66 cases of corn sensitivity. He makes the statement [12] that 1 of each 6 new patients in his office is found to be clinically sensi-

10. Randolph, T. G.: Fatigue and Weakness of Allergic Origin: To Be Differentiated from "Nervous Fatigue" or Neurasthenia, Ann. Allergy **3**:418, 1946; footnote 7.

11. Rinkel, H. J.: Migraine: Review of the Literature and Diagnostic Methods, Read Before the Southwest Allergy Forum, New Orleans, 1944.

12. Rinkel, H. J.: Personal Communication.

tive to corn; these figures are in close agreement with our series published in 1947.[4]

It should be stressed that in both of these series the occurrence of corn sensitivity was determined on the basis of precipitating observable clinical reactions following the experimental and deliberate ingestion of corn meal gruel and corn sugar in patients regularly ingesting corn products until the four day period of complete corn avoidance immediately prior to the performance of an individual food test with corn. It is to be reemphasized that the diagnosis of specific corn sensitivity in these cases was not made on the basis of the patient's suspicion of specific allergy or on the performance and mechanical interpretation of skin tests with extracts of corn. Scratch and intracutaneous tests with food allergens have been found so unreliable that such procedures have not been performed during the past six years.

The incidence of clinical allergy in the population at large is debatable, there having been but few surveys to establish this point.[13] One of us [14] tabulated the past and present evidence of allergic manifestations in a group of 140 student nurses and found that 60 per cent had a history of some unmistakable allergic response.

We are fully aware of the fact that patients with asthma are frequently treated with daily or continuous intravenous injection of dextrose and that many of them seem to tolerate this therapy without apparent adverse effects. One would not expect reactions to occur in the absence of corn sensitivity, and in a certain proportion of patients having low degrees of specific corn allergy, particularly if this was undiagnosed and corn in other forms was being taken as a part of the daily diet. From what is known of the mechanism and dynamic nature of food allergy,[3] one might expect the more acute clinical responses to occur in the recently diagnosed cases of corn allergy in which the patient had been avoiding the ingestion of this food for at least several days prior to the intravenous injection of corn sugar. It should be pointed out, however, that reactions in undiagnosed cases are known to occur, as illustrated in the second case of this series. Strosser [15] in 1932 also noted unfavorable responses to intravenous dextrose therapy consisting of nausea in some instances and vomiting in 2 patients. Sheldon[16]

13. Pipes, D. M.: The Incidence of Major and Minor Allergy in the Deep South, South. Med. J. **30**:1012, 1937. Vaughan, W. T.: Minor Allergy: Its Distribution, Clinical Aspects and Significance, J. Allergy **5**:184, 1933.

14. Randolph, T. G., and Hettig, R. A.: The Coincidence of Allergic Disease, Unexplained Fatigue and Lymphadenopathy: Possible Diagnostic Confusion with Infectious Mononucleosis, Am. J. Med. Sc. **209**:306, 1945.

15. Stoesser, A. V.: Recent Observations in the Study of Asthma Due to Food Allergy, J. Allergy **3**:332, 1932.

16. Sheldon, J. M.: Intravenous Use of Fluids in Bronchial Asthma, J. A. M. A., **139**:506 (Feb. 19) 1949.

recently reviewed this subject and concluded that the contraindications to the intravenous use of dextrose are few, mentioning Quattlebaum's [17] observation that a weakened mycoardium is jeopardized by the rapid increase in the blood volume which is produced as a result of the osmotic action of dextrose, speed shock and, finally, the production of anginal pain in some patients with angina pectoris. In his opinion these objections may be minimized if 5 per cent dextrose in distilled water is given slowly.

Inasmuch as the history of the patient is an unreliable index of whether or not he is sensitive to corn, specific allergy to maize must be suspected in all persons having the clinical characteristics suggestive of chronic food allergy.[8] It is probable that certain selected allergic persons meeting these criteria should be tested for the existence of corn sensitivity before being subjected to major surgical procedures necessitating the intravenous administration of corn sugar. At least in certain instances the presence of intravenous reactions of the type described might complicate the clinical picture in acutely ill patients. Furthermore, one should be alert to the possibility that nausea and vomiting in a given case may be manifestations of an allergic reaction. Should this happen to be on the basis of a specific allergic response to corn, as in the second case of this series, attempts to continue feeding corn suger intravenously are obviously contraindicated.

Finally, not all unexplained clinical reactions following the administration of glucose or dextrose are to be interpreted on the basis of pyrogen contamination or speed shock. The possibility of an allergic type of reaction in which the variability from normal exists in the patient rather than in the menstruum injected should be kept in mind.

SUMMARY

It is not generally appreciated that the dextrose employed intravenously is derived from the simple hydrolysis of corn starch, that the ingestion or intravenous injection of corn sugars commonly results in the production of allergic symptoms in at least some persons highly sensitive to corn and, lastly, that this phenomenon is not negligible in view of the fact that allergy to corn is currently a leading cause of chronic sensitivity to food.

Allergic responses resulting from the intravenous administration of corn sugar (dextrose) aid in the interpretation of some of the heretofore inexplicable reactions associated with such administration. It is also probable that the stormy postoperative course of certain allergic persons may be explained on this basis.

17. Quattlebaum, J. T.: Intravenous Therapy in the Treatment of Acute Heart Failure and Cardiac Asthma, J. South Carolina Med. A. **36**:354, 1947.

ADHESIONS RESULTING FROM REMOVAL OF SEROSA FROM AN AREA OF BOWEL

Failure of "Oversewing" to Lower Incidence in the Rat and the Guinea Pig

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IT HAS been a common clinical practice to "reperitonealize" areas of injury to the visceral peritoneum in order to prevent the formation of adhesions between such areas and omentum, intestine or other intra-abdominal structures. The usual method of doing this for serosal injuries to the bowel is to draw adjacent uninjured serosa together over the area of injury with interrupted sutures of a fine nonabsorbable material, such as 0000 silk, taking delicate bites of tissue with a small round-pointed needle.

Experiments carried out by Chandy in this laboratory have indicated that silk itself commonly becomes encapsulated by omentum and that the usual seromuscular stitch tied in place would, of itself, produce an adhesion in the experimental animal (rat).

EXPERIMENTAL STUDIES

The following experiments were carried out to see if the incidence of adhesions resulting from areas of bowel denuded of serosa was reduced or increased by oversewing.

The animals used in this work were 55 male albino rats weighing 250 Gm. which were bred in the Wistar Institute and 40 male guinea pigs of a similar weight. The procedures were first performed on rats and were then repeated with guinea pigs. This allows a comparison of the results in different species of animals and reduces the possibility that the adhesions produced were due to inherent characteristics of any one species.

Group A.—Organs similar in size, serosal covering and vascularity were selected for the procedures performed. These were the cecum in the rat and the terminal portion of small intestine just proximal to the cecum in the guinea pig. An area 0.5 cm. wide and 2 cm. long

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was denuded of serosa by carefully lifting the outermost covering of the bowel and peeling it off with fine toothless forceps. Every effort was made to avoid damage to the underlying tissues. The viscus was then replaced into the abdomen, and the peritoneum and muscle closed by a continuous, everting black silk suture. The skin was also closed by a continuous black silk suture.

Group B.—In this group of rats and guinea pigs, the selected site was stripped of serosa by means of the same technic and the denuded area was then oversewn with 0000 black silk on a small atraumatic needle. Four to six sutures were placed about 0.5 cm. apart, care being taken to avoid entering the lumen of the bowel so as to reduce the possibility of infection. The organ was replaced in the abdominal cavity and the abdominal wound closed as in group A.

If the bowel was accidently opened, the animal was not included in the experiment. In each animal the same amount of damage was performed so far as this was possible, and those in which the denuded area was left bare and those in which it was oversewn were selected at random by an independent observer after the denudation had been completed.

The animals were killed on the sixth day, and autopsy was performed. Adhesion formation is usually completed within three to six days after injury.[1] Only adhesions attached to the operative site were considered.

RESULTS [2]

Group A.—Of the 28 rats in this group, adhesions occurred from the bare area to adjacent bowel, abdominal wall, mesentery and peritoneal suture line in 8, or 28.5 per cent.

In the 19 guinea pigs included here, adhesions were found in 7, or 36.8 per cent.

Group B.—Adhesions were found in 20 of the 27 rats of this group in which the denuded area was oversewn, or 74 per cent.

Eighteen of the 21 guinea pigs included, or 85.7 per cent, showed adhesions to the sites mentioned under group A.

These figures indicate that in the 47 animals of both species in which the denuded area was not oversewn adhesions occurred in 15,

1. Richardson, E. H.: Studies on Peritoneal Adhesions, Ann. Surg. **54**:758, 1911. Coudry, E. V.: Textbook of Histology, Philadelphia, Lea & Febiger, 1934, p. 235. Hertzler, A. E.: The Peritoneum, St. Louis, C. V. Mosby Company, 1919, vol. 1, chapter on adhesions. Karsner, H. T.: Textbook of Human Pathology, Philadelphia, W. B. Saunders Company, 1936, chaps. 1 and 19.

2. Three rats and 2 guinea pigs included here died before the sixth postoperative day. Their exclusion would not materially affect the statistical analysis.

or 31.9 per cent, and in the 48 animals in which the denuded area was oversewn adhesions occurred in 38, or 79 per cent. A statistical analysis of these figures was performed with the use of the chi-square formula. It was found that the probability of obtaining this difference between groups A and B purely on the basis of chance is less than 1 per cent. Therefore, we consider these results significant.

Adhesion Formation in the Rat and the Guinea Pig Following Serosal Denudation of Areas of Bowel With and Without Oversewing

	Adhesions	No Adhesions	Percentage with Adhesions
Group A (not oversewn)			
Rat	8	20	28.5
Guinea pig	7	12	36.8
Total for both species	15	32	31.9
Group B (oversewn)			
Rat	20	7	74.0
Guinea pig	18	3	85.7
Total for both species	38	10	79.0

SUMMARY

In the rat and the guinea pig, the practice of oversewing an area of bowel which had been denuded of serosa more than doubled the incidence of adhesion formation to this area from 31.9 to 79 per cent.

In view of the recent observations of Brunschwig [3] on the regeneration of parietal peritoneum in man, the experiments reported here tend to cast doubt on the usefulness of oversewing areas of superficial injury to the visceral peritoneum in man. They do not apply to injuries involving the muscular coats of the bowel wall.

3. Robbins, G. F., Brunschwig, A., and Foote, F. W.: Deperitonealization: Clinical and Experimental Observations, Ann. Surg. **130**:466, 1949.

EXCRETORY UROGRAPHY VERSUS RETROGRADE UROGRAPHY

A Ureteral Compression Technic

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IT IS NOT the purpose of this paper to exploit the advantages and possibilities of each method of urography but rather to evaluate honestly the indications and contraindications for each. Braasch [1] summarized the matter well when he stated: "Although excretory and retrograde urography have individual advantages, they frequently are of complementary value and may be combined to good effect." We are in complete accord with this statement.

To Binz [2] goes the credit for having synthesized the iodine compound, which he called selectan neutral, that heralded the advent of excretory urography. Von Lichtenberg [3] was one of the first to use this substance clinically and to realize its possibilities. In his opinion, the compound called uroselectan (sodium iodomethamate), which also was synthesized by Binz and was similar to selectan neutral except that it contained less iodine and was more soluble, was even more adaptable for use in intravenous urography in that it is excreted in the urine in high concentration, gives good visualization and is nontoxic in the quantity necessary for intravenous injection.

During the years between 1929 and the present time compounds have been introduced which fulfil the criteria emphasized by von Lichtenberg much better than did uroselectan. While the scope of usefulness has widened, the number of limitations likewise has increased.

The technic of obtaining excretory urograms most certainly is not a standardized one. By reason of the many methods advocated, one is likely to be skeptical of them all; such has proved to be the case in all fields

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Read at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, June 9, 1949.

Dr. Oscar Zink and Dr. H. W. Frerking, of the Department of Radiology, St. Luke's Hospital, gave us valuable technical assistance.

1. Braasch, W. F.: Intravenous Urography, Surg., Gynec. & Obst. **51**:421 (Sept.) 1930.

2. Binz, A.: The Chemistry of Uro-Selectan, Brit. J. Urol. **2**:348 (Dec.) 1930.

3. von Lichtenberg, A.: The Principles of Intravenous Urography, Brit. J. Urol. **2**:341 (Dec.) 1930.

of medical science. The procedure which we follow is neither original nor perfect; nevertheless, we find that the percentage of diagnosable urograms is greater with this one than with any other which we have seen or used. Our plan is as follows: The patient is instructed to take castor oil the night prior to the morning we give the contrast medium. In addition, we restrict the intake of food by mouth for twelve hours before this time. The plain roentgenogram, or so-called K.U.B., is now taken, and we proceed with the injection of the contrast medium. In order to reduce to a minimum the chances of severe reaction, we always question the patient regarding a previous allergic history, and, furthermore, determine so far as possible the presence or absence of thyroid and hepatic disease. As to the actual intravenous injection of the medium, we introduce 1 cc. into the blood stream and then wait three

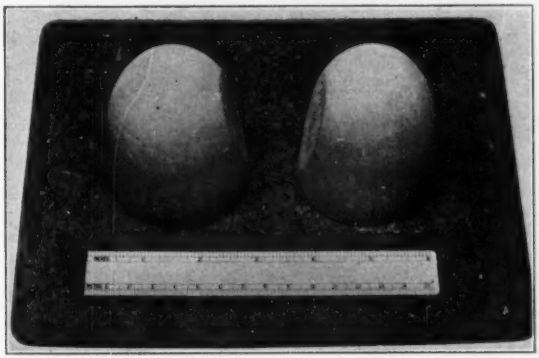

Fig. 1.—The masonite board with balsa wood cones attached, used for ureteral compression.

minutes. If no allergic manifestations appear, we proceed with the remainder of the intravenous injection.

Our experience with compression technics, in order to fill the renal pelves more completely, had been unsatisfactory until we began using a technic which employs the device shown in figure 1. Other types of apparatus such as rubber bags and plastic and wooden balls result in pressure over the promontory of the sacrum and not over the ureters, as is necessary.

The device which we use, shown in figure 1, is made simply of a masonite board 9 by 7 inches (22.8 by 17.7 cm.) with two balsa wood cones attached. These cones are 2¼ inches (5.7 cm., in diameter at the base and 2¾ inches (7 cm.) high and are separated ¾ inch

(1.91 cm.) at the base and 1¾ inches (4.4 cm.) at the apex. The cones are placed on the abdomen, some 3 inches (7 cm.) above the symphysis pubis, and then pressed into the abdominal cavity until the patient complains. The board is held in place by the compression band on the x-ray table. The purpose of all this, of course, is to obstruct the ureters at the point where they cross the brim of the pelvis and/or the common iliac arteries. That compression and subsequent ureteral

Fig. 2.—Excretory urogram of patient with large uterine fibroid, showing bilateral dilatation of pelves, calices and ureter. Note the excellent filling of both ureters.

obstruction produce more satisfactory urograms most certainly is demonstrated in patients who are pregnant or who have large pelvic tumors. Such a roentgenogram is seen in figure 2.

We find that roentgenograms taken five and ten minutes after injection, with the patient still prone, are most satisfactory, provided renal function is normal. Immediately after the ten minute roentgenogram

has been taken the patient is elevated to an upright position with the compression device still in place. Then with the cassette in place, the compression band is released and another roentgenogram taken at once. In this way we not only get information regarding the mobility of the kidneys but also usually fill the lower third of the ureters as well.

Obviously, delayed roentgenograms are best, even as long as two hours after injection, when there is impairment of renal function. In such a situation compression is not indicated or used. Delayed roent-

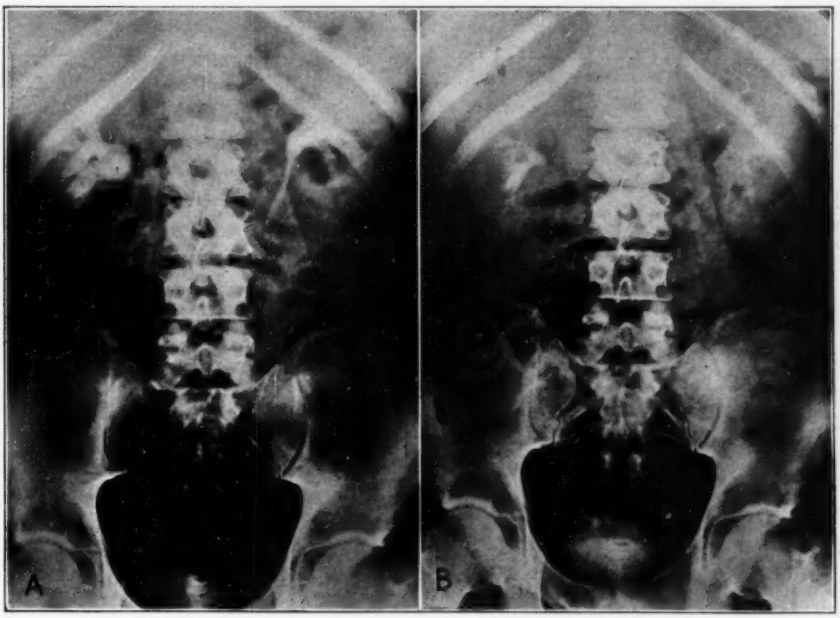

Fig. 3.—*A*, excretory urogram taken with compression apparatus in place. Note bilateral pelvic distention and ureteral filling. *B*, excretory urogram of same patient with compression released. Note the absence of pelvic distention.

genograms taken after the compression is released are at times valuable and necessary to determine the physiologic emptying time of the renal pelvis. These are taken with the patient in the upright position.

One can see in figures 3 and 4 the difference in the size and distention of the pelvis and calices in the roentgenograms taken before releasing the compression and afterward. To us this difference is too great to be explained merely as a difference between systole and diastole

of the pelvic musculature. We are convinced that since the adoption of this procedure the incidence of diagnosable urograms has increased 25 per cent.

The indications for obtaining such roentgenograms of the urinary tract have increased considerably since the method was first used and, in our opinion, rightly so. Perhaps one of their most important advantages is that they permit one to survey the entire urinary tract and thus direct attention to the diseased portion. In other words, the urologist can proceed more intelligently with a complete investigation without subjecting the patient to avoidable risks.

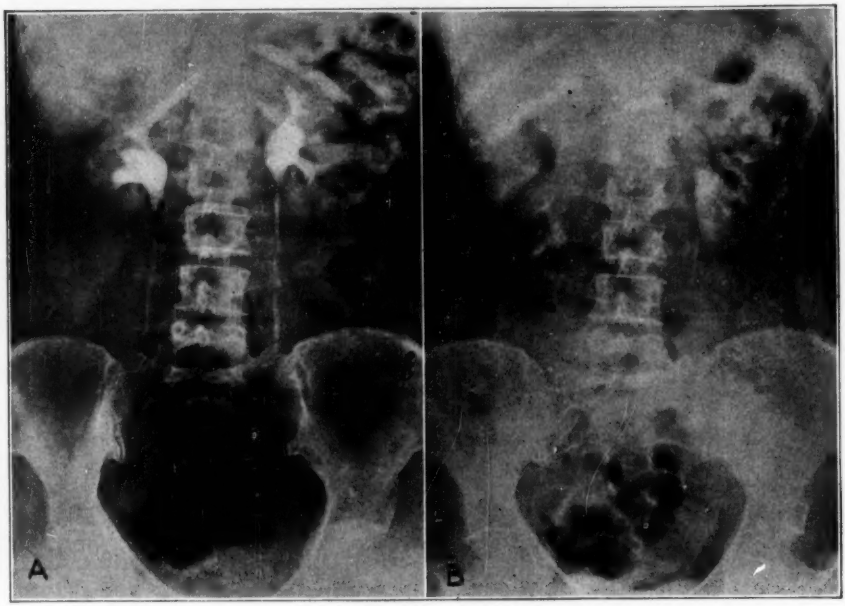

Fig. 4.—*A*, ureteral compression device in place. *B*, compression released.

An extremely important use of excretory urograms is the determination of renal function. A vast amount of material has been written regarding this subject, both for and against. In our experience, the method has proved valuable and in most cases reliable. If one notes the time of appearance of the contrast medium in the kidneys as well as the concentration, it is possible, we believe, to determine accurately individual renal function. In some cases the excreted contrast medium

does not remain in the pelvis and calices long enough to cast a good shadow. Therefore, one must note the concentration and appearance time of the contrast medium in the bladder before forming an opinion on the amount of function present.

In an excellent study on this subject Braasch and Emmett [4] found that in 39 of a series of 50 cases, or 78 per cent, in which both excretory urography and differential tests with indigo carmine were used the results of the two methods were in close agreement, while in 11 cases, or 22 per cent, the results did not agree. They stated that in cases of renal tuberculosis and calculous disease the excretory urogram is not reliable; yet, neither is indigo carmine.

We find that the most notable discrepancy in regard to renal function occurs in cases of the so-called cardiovascular-renal syndrome. In this condition one may find a complete absence of visualization, even in the presence of normal blood urea content. The explanation of this is not definite, but it seems to be due to the production of urine in such volume as to render the blood urea normal yet of such poor quality as to cast no shadow on the roentgenogram.

In a series of five hundred excretory urograms we have been entirely satisfied with this method as a test of renal function. In a small percentage of this series indigo carmine was used as well, and little if any additional information was obtained. We now use excretory urograms to the practical exclusion of all other methods of determining renal function.

It is in the search for a diagnosis of congenital anomalies that excretory urography is perhaps most useful. Since this diagnostic method was introduced, the incidence of urologic anomalies has increased considerably as shown by the number of cases reported in the literature. Crenshaw [5] emphasized the necessity of an excretory urogram in all cases of unexplained urinary incontinence. One must always keep in mind that a single segment of a complete duplication of pelves, calices and ureters can be nonfunctioning, and hence absence of visualization does not necessarily exclude duplication. Despite admitted deficiencies, excretory urography is of tremendous help in the diagnosis of congenital anomalies.

Intravenous urography is extremely helpful as well as satisfactory in the study of urinary calculi and subsequent damage to the urine passageways, as seen in figure 5 *A*. In our opinion this method is in many

4. Braasch, W. F., and Emmett, J. L.: Excretory Urography As a Test of Renal Function, J. Urol. **35**:630 (June) 1936.

5. Crenshaw, J. L.: Ureter with Extravesical Orifice: Supernumerary Ureter Ending Blindly; Crossed Ureteral Ectopia; Stones in Ureteropelvic Cystocele; Report of 11 Cases, J. Urol. **43**:82 (Jan.) 1940.

instances of more benefit for the exclusion or inclusion of questionable shadows than for ureteral catheterization and retrograde pyelograms. By means of the oblique roentgenogram, it is possible in most cases to identify positively all shadows in question, the only criterion for success being the presence of function on the part of the kidney sufficient to cast a positive shadow. Instrumentation and catheterization of the ureters and injection of contrast mediums may obscure completely small ureteral stones and those of low density in the pelvis and calices because

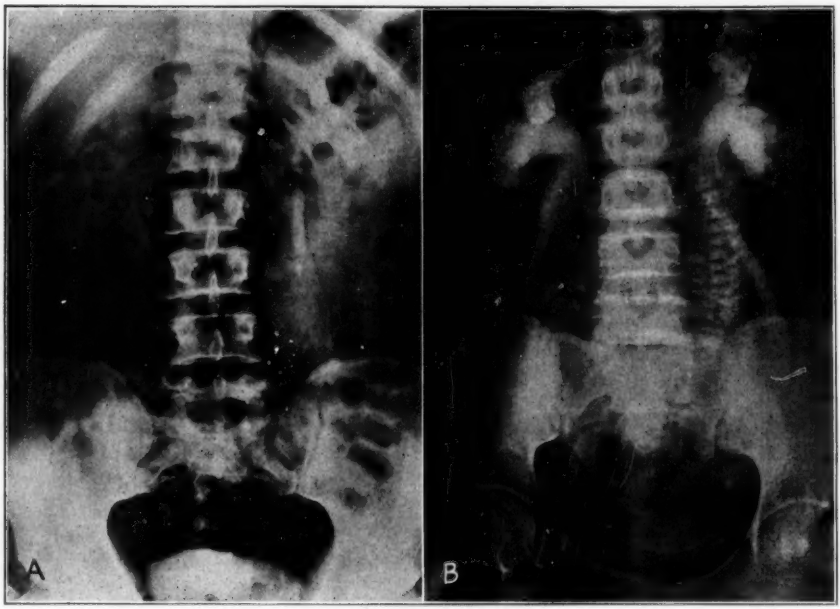

Fig. 5.—*A*, excretory urogram showing left ureteral calculus with ureteral dilatation and moderate hydronephrosis. *B*, excretory urogram which illustrates bilateral dilatation of pelves, calices and ureters as result of pregnancy.

of the extremely dense shadows cast by the catheter and pyelograms. Furthermore, one has added the risk of introducing bacteria into a stagnant pool of urine, such as that present behind an obstructed ureter, thereby changing a chronic situation into an extremely acute one, demanding in many instances immediate surgical intervention. As a result of this last fact we feel that every patient with ureteral colic should be given first the benefit of an excretory urogram, because if one does

make a diagnosis of ureteral calculus, the opportunity for conservative management is not necessarily lost, as it is in the majority of cases in which a ureteral catheter is introduced. Therefore we try to establish the diagnosis of a ureteral stone without the use of a ureteral catheter.

It is our belief that most cases of infection of the urinary tract, either of short or long duration, should be investigated by means of secretory urograms. This certainly can do the patient no harm, and it is amazing how often one finds a pathologic condition present in a kidney or ureter which obviously is the source of the infection. Particularly are urograms desirable in cases in which the Gram stain of the urinary sediment reveals the presence of organisms. Such urograms permit an intelligent treatment, and time is not lost through trying chemotherapy when obviously other measures are indicated, either prior to or in conjunction with the chemotherapy.

In the diagnosis of renal tuberculosis, excretory urography is becoming increasingly more important. This procedure permits one to determine which kidney is involved as well as the extent of involvement and is accomplished without subjecting the patient to repeated cystoscopy and ureteral catheterization and their attendant risks. Emmett and Braasch [6] stated: "A combination of excretory urography plus microscopic examination and staining the specimen of urine obtained by catheterization of the ureter of the so-called good kidney is no doubt the best procedure to follow at present."

Intravenous urography is being used extensively in the visualization of the upper portion of the urinary tract during pregnancy. This can be seen in figure 5 *B*. After the third month one invariably finds the renal pelves and the upper part of the ureters well filled as a result of lower ureteral obstruction from the enlarging uterus; hence, any extra-abdominal compression is contraindicated. The best filling usually is present in the delayed roentgenograms. Generally the diagnostic information procured is sufficient to permit one to handle the matter intelligently with little or no risk to the mother. We have observed no ill effect on babies delivered from mothers subjected to secretory urograms. In no instance did the patient abort. Our experiences seem to coincide with those outlined by Woodruff and Milbert.[7]

It was in the field of pediatric urology that excretory urography originally was thought to offer the greatest possibilities. We believe that the procedure has a definite place in the diagnostic work-up in

6. Emmett, J. L., and Braasch, W. F.: Has Excretory Urography Replaced Retrograde Pyelography in the Diagnosis of Renal Tuberculosis? J. Urol. **40**:15 (July) 1938.

7. Woodruff, S. R., and Milbert, A. H.: Roentgenographic Studies of Urinary Tract During and After Pregnancy, J. A. M. A. **111**:1607 (Oct. 29) 1938.

children, not in any sense to the exclusion of instrumentation and retrograde pyelograms but rather as one essential part of the examination. A notable discrepancy can be seen easily between figures 6 *A* and 6 *B*. The excretory urogram certainly does not reveal the amount of dilatation as depicted by the retrograde pyeloureterogram. One always should keeps this fact in mind when evaluating the urinary system in children in whom there is an inherent neuromuscular weakness.

This estimate, of course, falls short of the expectations of some of the original workers. Teall [8] expressed the matter well. He writes:

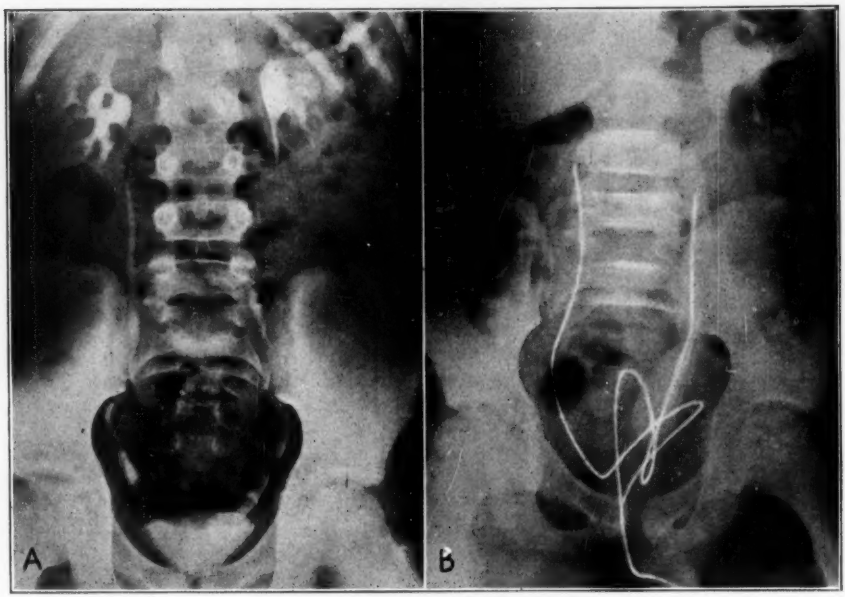

Fig. 6.—*A*, comparatively normal excretory urogram except for mild ureterectasis in lower third of each ureter. *B*, left retrograde pyeloureterogram of same patient. Note considerable ureteral dilatation.

"Intravenous urography in children has not replaced the retrograde method, for the limitations of intravenous urography are the same in children as in adults."[9] Children tolerate the iodides well, and we have

8. Teall, C. G.: Intravenous Urography in Children, Brit. M. J. **2**:788 (Oct. 29) 1932.

9. Information on the subject is also given by Baker (Baker, W. J.: Evaluation of Retrograde and Intravenous Pyelography, Surg., Gynec. & Obst. **71**:540 [Dec.] 1940).

noted no untoward systemic reactions. The method certainly has increased the recognition of anomalies in children, and, if for no other reason, this fact makes it invaluable. Technically, excretory urography in children is not difficult, if one uses the proper amount of sedation. We find that the barbiturates, given by rectum, are most helpful. Infants should be given a general anesthesia before the intravenous urogram

Fig. 7.—Excretory urogram showing extravasation of contrast medium as a result of renal trauma.

is made. If necessary, proceed immediately with the cystoscopic examination, cystograms and retrograde pyelograms.

We are of the opinion that all patients suspected of having an injury of the urinary tract should be given the benefit of an excretory urogram immediately after the history has been elicited and the physical examination and urinalysis carried out. The risk involved, even in the presence of injury, is negligible, and the information obtained is invaluable, as

shown in figure 7, be the injury one of kidney, ureter or bladder. It is true that there may be a complete absence of visualization on one side, but, knowing this fact, one can proceed more intelligently with the examination.

In the diagnosis of tumors of the urinary tract we have found that excretory urograms are extremely valuable. It is the rule rather than the exception that renal tumors can be diagnosed by this method if sufficient function remains to visualize the kidney. It is our practice,

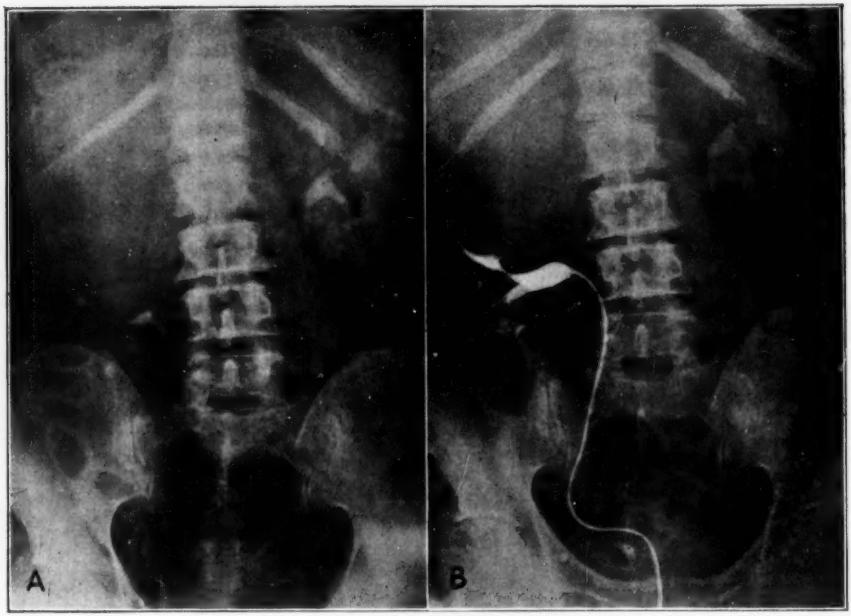

Fig. 8.—*A*, excretory urogram showing deformity suggestive of right renal tumor. *B*, right retrograde pyelogram confirming the suggestive renal tumor shown in *A*.

however, to confirm these findings with a retrograde pyelogram if possible. Figure 8 illustrates such a case. Obstruction to excreted contrast medium in the ureters, along with filling defects in both excretory ureterograms and cystograms, is another important advantage of this method.

A good nephrogram is obtained frequently as a result of secretory urography. This is helpful in the diagnosis of renal tumors. Braasch

and Emmett stated that excretory urography can suggest the amount of function remaining in the kidneys which are the seat of malignant tumors but cannot be relied on to predict the extent of neoplastic involvement.

In men with enlarged prostates, particularly those with intravesical median hypertrophy, the ureteral orifices are at times completely invisible cystoscopically. The upper part of the urinary tract can be studied only

Fig. 9.—Excretory urogram showing large filling defect due to intravesical prostatic enlargement, in addition to normal renal function and configuration.

by excretory urography (fig. 9). A similar situation likewise is encountered in patients who are subjected to ureterosigmoidostomy and total cystectomy (fig. 10). In the latter we find that the value for the blood urea compares favorably with the appearance time and concentration of the contrast medium as a test of renal function.

It is at times unwise to catheterize the urethra in order to determine the presence or absence of residual urine. One can procure the same

information by having the patient void after an excretory urogram has been made and by taking a final picture to see if any contrast medium remains in the bladder.

The contraindications for excretory urography are not great if one will distinguish factors which prevent prompt, adequate visualization from those which actually constitute a risk to the patient. Obviously, such factors as uremia, cardiovascular renal disease and marked abdominal distention prevent one from obtaining diagnostic roentgenograms. Decreased hepatic function, hyperthyroidism and iodine sensi-

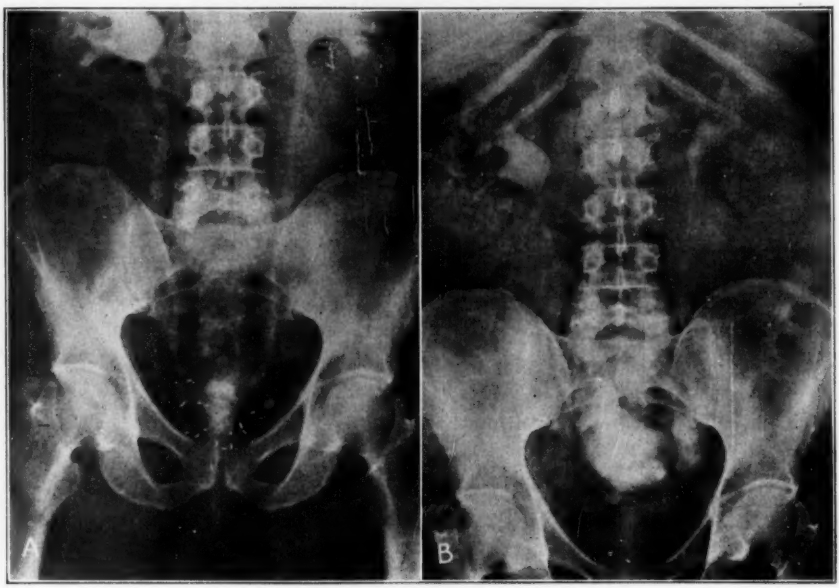

Fig. 10.—*A*, preoperative excretory urogram with bilateral dilatation. Note well filled ureters and radon seeds in contracted bladder with carcinoma. *B*, excretory urogram of postoperative ureterointestinal anastomosis (same patient as seen in *A*).

tivity constitute a group of conditions in which the intravenous administration of the iodine compounds used for excretory urography may cause additional damage and even death.

The reader by this time may have gained the impression that we advocate only rarely the use of retrograde pyelography. This most certainly is not the case. As previously stated, our practice rather is to combine the two methods and make retrograde pyelograms of all patients

on whom additional information is required. We prefer to think of the two methods as individually advantageous and not in the least a duplication of effort, even when used on the same patient on the same day.

The two major reasons for retrograde urography are, first, the necessity for more detailed information about the drainage system of the urinary tract whether it be of calices, pelves, ureters or bladder and, second, the initial visualization of the pelviocaliceal system in which the kidney is nonfunctioning. There are, of course, many other reasons for ureteral catheterization, but for the purpose of diagnosis retrograde urography can be used.

There are contraindications to retrograde urography as well as to excretory urography. Here again one must distinguish between factors which prevent the retrograde pyelograms being accomplished, such as the inability to pass a cystoscope and catheterize the ureters, and conditions which jeopardize the safety of the patient. It is the contraindications involving a risk with which we are most concerned. First of all, a cystoscopic examination and retrograde pyelograms should not be attempted on debilitated patients unless the information to be obtained justifies the risk. Catheterization of ureters and subsequent pyelograms of a hydronephrotic kidney usually will result in severe systemic reactions. Retrograde pyelography, especially bilateral, should not be done in cases of nephritis. It is believed that miliary tuberculosis has resulted in some instances from retrograde pyelograms being made of a tuberculous kidney.

In the final analysis of the problem, one can state that neither method is without risk, but if the candidate is chosen carefully, this risk is negligible indeed.

CONCLUSIONS

1. The method of compressing the ureters during the making of excretory urograms has resulted in a higher percentage of diagnosable urograms.

2. Excretory urography directs one's attention to the diseased part of the urinary system.

3. In tests for renal function the use of the excretory urogram is highly satisfactory.

4. The recognition of congenital anomalies has increased since intravenous urography has been more widely accepted.

5. A more conservative management of urinary calculi is possible if the diagnosis of the stone has been made from an excretory urogram.

6. Study of the urinary tract by secretory methods has proved advantageous in all types of infections.

7. Excretory urography in children is valuable, but usually retrograde studies also are indicated.

8. Diagnoses of injuries of the urinary tract are best made by means of the excretory urograms.

9. Usually retrograde pyelograms should be obtained before a diagnosis of a renal tumor is made and always before operation is performed.

10. An excretory urogram is the only means of visualizing the upper part of the urinary tract after ureterointestinal anastomosis. This is likewise true of benign prostatic hypertrophy in many cases.

11. There is a risk involved with either secretory or retrograde urography, but if the subject is selected carefully this risk is almost negligible.

3720 Washington Avenue.

PRESENT DAY METHODS OF DISINFECTING THE SKIN

Survey of Disinfectants and Technics Currently Employed in the Hospitals of the United States and Canada

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THE INCOMPLETELY solved problem, disinfection of the skin, remains a relatively weak link in the chain of surgical technic. Methods used to disinfect hands and fields of operation vary from hospital to hospital. Many surgeons and operating room supervisors have adopted routine procedures which one suspects are based more on tradition, chance recommendation or drug house salesmanship than on scientific evaluation.

Behind this diversity of practice lies a singular lack of agreement among those who write on the subject. Even investigators who approach the problem experimentally often reach divergent conclusions, largely because there are no generally accepted uniform methods for testing skin disinfectants.

The practice of surgery would be benefited, and its standards would be elevated, if order could be brought out of this chaos and if some council or commission would undertake a study of the problem and emerge with an unbiased, authoritative pronouncement regarding (1) acceptable standard methods of testing germicides and their effects under conditions of actual use, (2) relative merits of the commonly used skin disinfectants and (3) specific recommendations as to their routine employment in office, ward and operating room.

In order to envision the problem more clearly, information concerning surgical technics in use at the present time was obtained by questionnaire from the operating room supervisors of one hundred hospitals in the United States and Canada. The hospitals (table 1) were carefully selected and are believed to be fairly representative of American hospitals generally.

PREPARATION OF THE HANDS FOR OPERATION

The Scrub.—All the reporting hospitals still [1] employ the traditional scrub. From three to ten minutes are required for this step.

Chemical Disinfection.—Tables 2 and 3 indicate the variety of agents and solutions used in different hospitals at the present time. Although

From the Department of Surgery, University of Utah College of Medicine.

1. This survey was completed in September 1948.

TABLE 1.—*Analysis of Hospitals Supplying Information*

Geographic Distribution		Number of Hospitals
New England		5
Northeastern states		26
Southern states		22
Midwestern states		35
Mountain states		5
Pacific states		5
Canada		2
		100
Size of Hospitals		
Less than 100 beds		12
101 to 300 beds		30
301 to 600 beds		32
601 to 1,000 beds		13
Over 1,000 beds		13
		100
Ownership and Control		
Federal		10
United States Public Health Service	1	
Veterans Administration	6	
Army	1	
Navy	1	
Marine	1	
State		11
County		7
City		9
Church operated or affiliated		11
Nonprofit corporations		50
Privately owned		2
		100
Type of Hospital		
University		22
Other teaching hospitals		8
Nonteaching general hospitals		64
Children's		2
Psychopathic		1
Tuberculosis		2
Homeopathic		1
		100

TABLE 2.—*Solutions Currently Used to Disinfect the Hands for Operation*

Solutions		Percentage of Hospitals in Which They Are Used
Ethyl alcohol only		60
Alcohol or zephiran * chloride		2
Ethyl alcohol preceded or followed by another disinfectant		21
Iodine (for finger tips)	3	
Mercurial solution	10	
Lime and soda	1	
Lysol	1	
Zephiran * chloride	6	
Mercuric chlorides only		2
Zephiran * chloride only		12
Aqueous	8	
Tincture	4	
Isopropyl alcohol		2
None (10 minute scrub only)		1
		100

* Registered trademark.

70 per cent ethyl alcohol is by far the most frequently used preparation, it is not specified in most of the replies whether the percentage indicated is by volume or by weight. The concentrations of mercurial solutions employed also vary as follows: mercuric chloride, 1:1,000, 1:3,000 and 1:4,000; potassium mercuric iodide, 1:1,000 and 1:5,000; mercuric cyanide, 1:1,000 and 1:2,000. One hospital uses 40 per cent isopropyl alcohol solution, while another uses a 50 per cent solution. One hospital apparently employs no chemical hand disinfectants at all but depends entirely on a ten minute scrub.

Methods of Use.—In fifty-nine hospitals the hands and arms are washed or are "soaked" in basins containing the disinfectant solution. The wash in these basins ranges from a "dip" to a ten minute soak. Six

TABLE 3.—*Preparations of Ethyl Alcohol Currently Used to Disinfect the Hands for Operation*

Strength of Solutions		Percentage of Hospitals in Which They Are Used
50 per cent		2
60 per cnet		2
65 per cent		1
70 per cent		73
"By volume"	1	
"By weight"	3	
Unspecified	69	
75 per cent		1
80 per cent		1
95 per cent		2
"Alcohol" (unspecified strength)		1
		83

of the hospitals use "dispensers" in the operating room, and nineteen use sprays of some sort to apply the disinfectant to the hands. Replies from sixteen of the hospitals fail to indicate how hand disinfectants are used.

PREPARATION OF THE FIELD OF OPERATION

The custom of washing and shaving the area of operation on the ward several hours or the day before the patient is sent to the operating room is doubtless a prevalent one but just how prevalent the replies to the questionnaire do not clearly indicate. In thirty-six of the one hundred hospitals polled, the site of operation is washed (again?) with soap and water in the operating suite immediately before operation.

Chemical Disinfection.—In most operating rooms two or three different disinfectant solutions are used in succession to disinfect the field of operation. A popular combination, for example, is 70 per cent alcohol, then ether and then tincture of merthiolate® (sodium ethylmercurithiosalicylate). In some large hospitals many different solutions

are kept available in the operating room since each operator or service may prefer some particular disinfectant or combination of disinfectants. Table 4 indicates the wide variety of preparations in current use.

TABLE 4.—*Preparations Used to Disinfect the Skin of the Field of Operation*

Preparations		Percentage of Hospitals in Which They Are Used
Ether		68
Ethyl alcohol		64
60 per cent	2	
70 per cent	49	
75 per cent	1	
80 per cent	1	
95 per cent	2	
Unspecified strength	9	
Merthiolate *		55
Tincture 1: 1,000	43	
Aqueous 1: 1,000	1	
Unspecified	11	
Zephiran * chloride		48
Tincture	37	
Aqueous	8	
Unspecified	3	
Iodine		20
0.1 per cent	2	
0.5 per cent	3	
2.0 per cent	2	
2.5 per cent	1	
3.5 per cent	8	
7.0 per cent	1	
Unspecified strength	3	
Mercresin *		7
Tincture, 1: 1,000	6	
Modified solution	1	
Metaphen *		6
Tincture, 1: 200	1	
Tincture, 1: 1,000	1	
Tincture, unspecified	2	
Aqueous, unspecified	2	
Mercuric chloride		6
Novak's solution	3	
Harrington's solution	2	
Aqueous, 1: 4,000	1	
Miscellaneous		
Phemerol * chloride, various preparations		5
Isopropyl alcohol, various strengths		3
Ceepryn * chloride, various preparations		3
Mercurochrome * (Scott's solution)		2
Lime and soda		1
Benzene		1
Chrysodin Y		1
"Kalmerid" (potassium mercuric iodide), in acetone		1
Hexachlor-m-cresol skin solution		1
"Antiseptic septisol"		1
"Mark 'S' solution"		1

* Registered trademark.

Methods of Application.—Only 4 per cent of the hospitals use sprays to apply disinfectant solutions to the field of operation; the remainder "paint" the solutions on with gauze sponges.

DISINFECTION OF CONTAMINATED HANDS

Methods currently used to disinfect contaminated hands on the wards are equally heterogeneous. Tables 5 and 6 list the agents used. The time spent in washing the hands is not stated in some of the replies, while others specify one, two and even five minute washes. One hospital requires a hand "soak" in a 1 : 1,000 mercuric chloride solution, whereas another requires a "dip" in a 1 : 10,000 solution of the same agent.

TABLE 5.—*Methods Currently Used on Wards to Disinfect Contaminated Hands*

Methods	Percentage of Hospitals in Which They Are Used
Hands simply washed with soap and water	16
Hands scrubbed with brush, soap and water	18
Hands rinsed with water, followed by disinfectant solution	1
Hand wash (with soap) followed by disinfectant solution	12
Hand scrub followed by disinfectant solution	31
Chemical disinfection without preliminary wash	20
No report	3
	100

TABLE 6.—*Solutions Currently Used on Wards to Disinfect Contaminated Hands*

Solutions		Percentage of Hospitals in Which They Are Used
Ethyl alcohol		37
50 per cent	1	
"70 per cent"	33	
Unspecified strength	3	
Zephiran * chloride		14
Aqueous, 1: 1,000	4	
Tincture, 1: 1,000	4	
Unspecified	6	
Lysol (various strengths)		10
Mercuric chloride (various strengths)		3
Isopropyl alcohol, 50 per cent		1
Cresol, 1.5 per cent		1
Mercuric cyanide, 1: 2,000		1
Lime and soda		1
Miscellaneous proprietary preparations		5

* Registered trademark.

Strengths of lysol solutions used range from 0.25 per cent to 5 (sic!) per cent. Most of the replies do not indicate how these disinfectants are applied, whether by means of sprays, dispensers or solution basins.

SUMMARY

A questionnaire survey of one hundred representative hospitals in the United States and Canada shows that a great many different methods and agents are used at the present time in attempts to disinfect the skin, whether it be the hands preoperatively, the skin of the site of operation or

contaminated hands on wards. The reason for this diversity of practice is not so much that all agents and methods are equally good or poor but that there are no generally accepted standard tests by which to evaluate skin disinfectants. The clinical test of the presence or absence of subsequent gross infection is a crude one; taken alone, it is the result of so many uncontrollable variables that it is usually without significance.

The general level of surgical technic would be raised and much confusion would be eliminated by the following measures: (1) adoption of standard methods of testing skin disinfectants under conditions of actual use, (2) an authoritative evaluation of the commonly used skin disinfectants on the basis of such tests and (3) specific recommendations as to their proper use in operating room, ward and office.

NEW SIMPLIFIED TECHNIC FOR LOCALIZATION OF FOREIGN BODY

LOUIS W. BRECK, M.D.
AND
DONALD J. MAYLAHN, M.D.
EL PASO, TEXAS

IN RECENT years a multitude of methods for localizing foreign bodies has filled both the American and the foreign literature, but the majority require special localizing equipment. The methods described have been based on some form of localization or on electronic principles. One method of localization is based on the basic principle of parallax and similar triangles as popularized by Shenton.[1] The depth of the foreign body is determined from measurement of its shift on parallel x-ray plates when the tube head is shifted and a double exposure is made on the roentgenograms.[2] A second method is based on the principle of marking the skin with gentian violet at intervals of 1 inch (2.5 cm.), placing lead shot on adhesive tape along the same lines and taking a roentgenogram.[3] A third method is the localization of foreign bodies with a pointed hemostat under the fluoroscope. The electronic metal locator is based on the principle of the Hughes balance and was popularized by Samuel Berman and modified by Gilson and Erickson.[4] A metal probe is connected to an electronic amplifier which produces a sound when the tip is near a metallic foreign body.

A new method will be described in this paper wherein a small metal clip, fashioned from malleable wire, is placed in the wound under direct vision and the foreign body is localized in relation to it by means of anteroposterior and lateral roentgenograms. This new method has many desirable points. Simplicity is foremost, since the only special equipment

1. Shenton, E. W. H.: A New Method of Rapid X-Ray Localization, Guy's Hosp. Gaz. **30**:87 (March) 1916; X-ray Localization of Foreign Bodies, Brit. M. J. **1**:993 (June 15) 1940.

2. Moore, J. J., and Loehr, W. M.: Roentgenographic Method for Localization of Foreign Bodies, Bull. U. S. Army M. Dept. **88**:104-111 (May) 1945. Westing, S. W.: A Method of Foreign Body Localization Using Two Parallel Roentgen Films, Am. J. Roentgenol. **53**:189-193 (Feb.) 1945.

3. Wilton, T. N. P.: A Rapid Method of Locating Shell Fragments, Using X-Rays, Brit. M. J. **1**:637-638 (May 5) 1945.

4. Gilson, W. E., and Erickson, T. C.: A New Surgeon's Metal Locator, Mil. Surgeon **97**:508-512 (Dec.) 1945.

required is a short piece of malleable wire, in contrast to other methods which require special x-ray machines, localizing apparatus or electronic locators. Speed and accuracy are achieved because the localization is done under direct vision with the aid of roentgenograms made with an ordinary portable x-ray unit. There is a minimum of trauma to the tissue because the foreign body is accurately localized in relation to the clip deep in the wound and extensive dissection is unnecessary. This eliminates the large amount of probing and cutting required when the foreign body is localized to a marker on the skin surface. Another most important feature is the negligible amount of irradiation to which the surgeon is subjected during the localization process. We believe that fluoroscopy is contraindicated in the localization of foreign bodies because of the danger of burns. An advantage which this technic has over the electronic metal locator is that it can be used not only for metallic foreign bodies but also for those of lead containing glass.

METHOD

A routine anteroposterior and lateral roentgenogram of the involved region is made on the patient's admission to the hospital. The patient is then taken to the operating room, and after the routine preparation of the skin and draping, a short linear cutaneous incision is made over the site of the foreign body. The incision is developed through anatomic planes to the approximate region of the foreign body, and the latter is looked for superficially. A small metal clip is then fashioned from a short piece of heavy malleable wire such as stainless steel bone wire and clipped firmly to the soft tissue in the region of the foreign body. Under sterile precautions, with the use of sterile cassette covers, anteroposterior and lateral roentgenograms are made. After examination of these, one determines the position of the foreign body in relationship to the metal clip. The foreign body is then carefully looked for. If its position, as in figure 1, is slightly proximal, lateral and deep to the clip, it is searched for in this general area with a minimal amount of dissection and probing. If it is not readily found, the clip is moved in the direction of the approximate location and new anteroposterior and lateral roentgenograms are made. The foreign body is again localized in reference to the metal clip, and figure 2 reveals how close one can place the clip to it on the second attempt. The process is repeated as often as is necessary to localize the foreign body for final extraction. In almost all cases, one or at most two clip placements and accompanying sets of roentgenograms are required for accurate localization of a foreign body. This method has been used a considerable number of times with facility and satisfaction. One case will be reported which would have been extremely difficult without a satisfactory localizing technic.

Fig. 1.—Roentgenograms made after initial placement of metal clip for localization of foreign body.

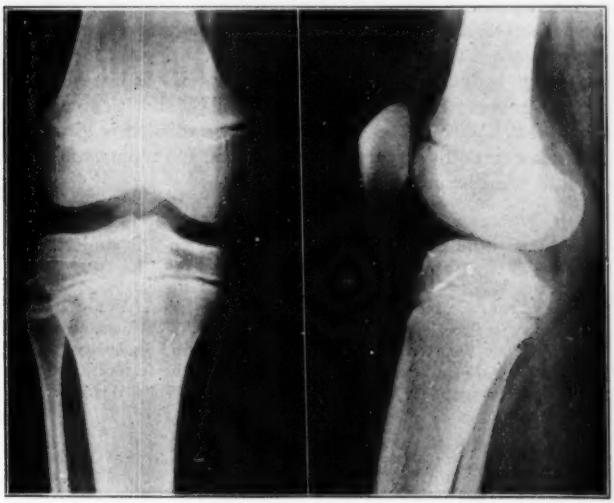

Fig. 2.—Roentgenograms made after final placement of metal clip for localization of foreign body.

REPORT OF A CASE

On Dec. 17, 1947, a 9 year old girl was running at home and fell on a needle. The point of entry was anterior, just below the left knee joint line. An attempt to extract the needle at home caused it to break off, and the patient sought medical care because of pain throughout the entire left knee.

Physical examination revealed tenderness all about the knee joint, primarily below the joint line anteriorly. The point of entrance of the needle was anterior, just below the joint line and slightly medial. Anteroposterior and lateral roentgenograms of the left knee revealed the eye of a needle, 5 mm. in length, in the region of the knee joint slightly below the joint line and anteriorly.

The patient was taken to the operating room, and under a tourniquet and general anesthesia a linear incision was made on the anteromedial aspect of the leg just below the joint line. The metal clip was clipped to the soft tissue, and anteroposterior and lateral roentgenograms were made (fig. 1). These revealed the foreign body lying lateral, proximal and deep to the metal clip. The incision was developed in this direction and the foreign body searched for. It was not located readily, so the clip was moved closer to it and another set of roentgenograms was made (fig. 2). After the second localization the foreign body was found embedded in the bone flush with the surface, with only the end section visible. It was removed and the wound closed. The total operating time was one hour, and only two sets of roentgenograms were required. There was an uneventful postoperative course, and the patient was discharged from the hospital. There was complete function of the left knee in three weeks.

SUMMARY

A new method of localizing radiopaque foreign bodies is described, employing a small clip made of heavy metal wire which is placed in the tissues under direct vision near the foreign body and localized with roentgenograms. This gives a landmark for localizing the foreign body. If the foreign body is not easily found, the clip may be moved closer to it and the procedure repeated. The method is simple, accurate and relatively fast. With its use, a minimum of irradiation is given to the patient and none to the surgeon, and exploration and trauma to the tissue are kept at a minimum.

The references mentioned above, along with those given in the final footnote,[5] constitute key articles in the literature on this subject.

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5. Berman, L. G.; Sahler, O. D., and Radow, I. B.: Foreign Body Localization and Surgery, Am. J. Roentgenol. **57**:766-769 (June) 1947. Brailsford, J. F.: Localization of Foreign Bodies, Lancet **2**:749-751 (Dec. 9) 1944. Jamison, H. W.: A Simple Accurate Fluoroscopic Method of Foreign Body Localization, Radiology **47**:397-398 (Oct.) 1946. Sempe, Un appareil radioscopique de repérage des corps étrangers simple et pratique, J. de radiol. et d' électrol. **28**:109-111, 1947.

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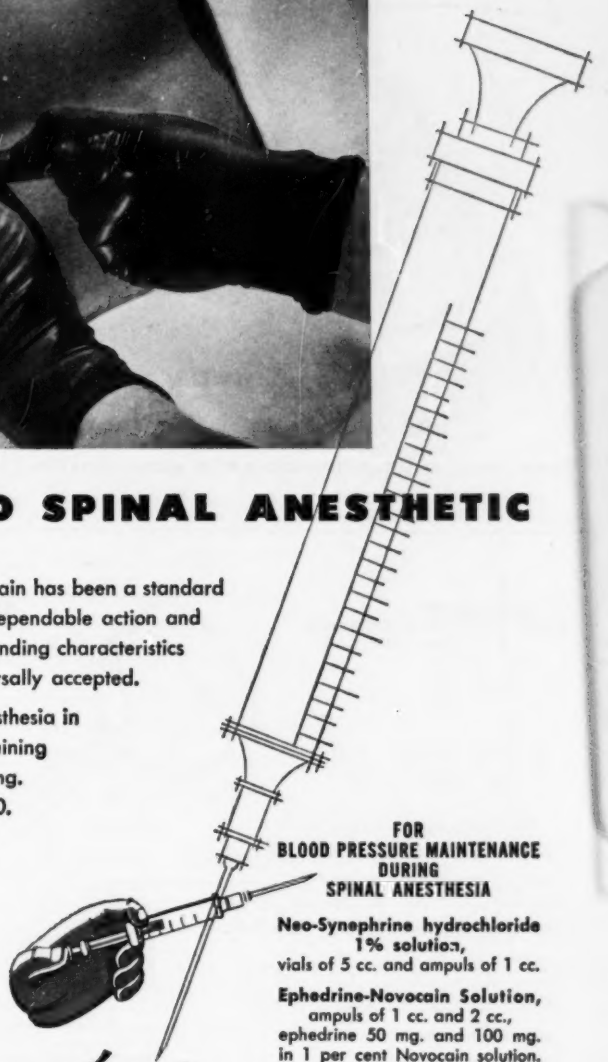

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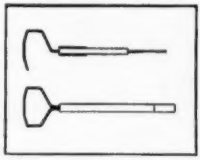

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